Annu. Rev. Psychol. 2006. 57:87–115
doi: 10.1146/annurev.psych.56.091103.070229

First published online as a Review in Advance on September 16, 2005

BEHAVIORAL THEORIES AND THE NEUROPHYSIOLOGY OF REWARD

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Key Words learning theory, conditioning, microeconomics, utility theory, uncertainty

■ **Abstract** The functions of rewards are based primarily on their effects on behavior and are less directly governed by the physics and chemistry of input events as in sensory systems. Therefore, the investigation of neural mechanisms underlying reward functions requires behavioral theories that can conceptualize the different effects of rewards on behavior. The scientific investigation of behavioral processes by animal learning theory and economic utility theory has produced a theoretical framework that can help to elucidate the neural correlates for reward functions in learning, goal-directed approach behavior, and decision making under uncertainty. Individual neurons can be studied in the reward systems of the brain, including dopamine neurons, orbitofrontal cortex, and striatum. The neural activity can be related to basic theoretical terms of reward and uncertainty, such as contiguity, contingency, prediction error, magnitude, probability, expected value, and variance.

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INTRODUCTION

How can we understand the common denominator of Pavlov's salivating dogs, an ale named Hobgoblin, a market in southern France, and the bargaining for lock access on the Mississippi River? Pavlov's dogs were presented with pieces of delicious sausage that undoubtedly made them salivate. We know that the same animal will salivate also when it hears a bell that has repeatedly sounded a few seconds before the sausage appears, as if the bell induced the well-known, pleasant anticipation of the desired sausage. Changing slightly the scenery, imagine you are in Cambridge, walk down Mill Lane, and unfailingly end up in the Mill pub by the river Cam. The known attraction inducing the pleasant anticipation is a pint of Hobgoblin. Hobgoblin's provocative ad reads something like "What's the matter Lager boy, afraid you might taste something?" and refers to a full-bodied, dark ale whose taste alone is a reward. Changing the scenery again, you are in the middle of a Saturday morning market in a small town in southern France and run into a nicely arranged stand of rosé and red wines. Knowing the presumably delicious contents of the differently priced bottles to varying degrees, you need to make a decision about what to get for lunch. You can do a numerical calculation and weigh the price of each bottle by the probability that its contents will please your taste, but chances are that a more automatic decision mechanism kicks in that is based on anticipation and will tell you quite quickly what to choose. However, you cannot use the same simple emotional judgment when you are in the shoes of an economist trying to optimize the access to the locks on the Mississippi River. The task is to find a pricing structure that assures the most efficient and uninterrupted use of the infrastructure over a 24-hour day, by avoiding long queues during prime daytime hours and inactive periods during the wee hours of the night. A proper pricing structure known in advance to the captains of the barges will shape their decisions to enter the locks at a moment that is economically most appropriate for the whole journey. The common denominator in these tasks appears to relate to the anticipation of outcomes of behavior in situations with varying degrees of uncertainty: the merely automatic salivation of a dog without much alternative, the choice of sophisticated but partly unknown liquids, or the well-calculated decision of a barge captain on how to get the most out of his money and time.

The performance in these tasks is managed by the brain, which assesses the values and uncertainties of predictable outcomes (sausage, ale, wine, lock pricing, and access to resources) and directs the individuals' decisions toward the current

optimum. This review describes some of the knowledge on brain mechanisms related to rewarding outcomes, without attempting to provide a complete account of all the studies done. We focus on the activity of single neurons studied by neurophysiological techniques in behaving animals, in particular monkeys, and emphasize the formative role of behavioral theories, such as animal learning theory and microeconomic utility theory, on the understanding of these brain mechanisms. Given the space limits and the only just beginning neurophysiological studies based on game theory (Barraclough et al. 2004, Dorris & Glimcher 2004), the description of the neurophysiology of this promising field will have to wait until more data have been gathered. The review will not describe the neurobiology of artificial drug rewards, which constitutes a field of its own but does not require vastly different theoretical backgrounds of reward function for its understanding. Readers interested in the rapidly emerging and increasingly large field of human neuroimaging of reward and reward-directed decision making are referred to other reviews (O'Doherty 2004).

GENERAL IDEAS ON REWARD FUNCTION, AND A CALL FOR THEORY

Homer's Odysseus proclaims, "Whatever my distress may be, I would ask you now to let me eat. There is nothing more devoid of shame than the accursed belly; it thrusts itself upon a man's mind in spite of his afflictions. . .my heart is sad but my belly keeps urging me to have food and drink. . .it says imperiously: 'eat and be filled'." (*The Odyssey*, Book VII, 800 BC). Despite these suggestive words, Homer's description hardly fits the common-sensical perceptions of reward, which largely belong to one of two categories. People often consider a reward as a particular object or event that one receives for having done something well. You succeed in an endeavor, and you receive your reward. This reward function could be most easily accommodated within the framework of instrumental conditioning, according to which the reward serves as a positive reinforcer of a behavioral act. The second common perception of reward relates to subjective feelings of liking and pleasure. You do something again because it produced a pleasant outcome before. We refer to this as the hedonic function of rewards. The following descriptions will show that both of these perceptions of reward fall well short of providing a complete and coherent description of reward functions.

One of the earliest scientifically driven definitions of reward function comes from Pavlov (1927), who defined it as an object that produces a change in behavior, also called learning. The dog salivates to a bell only after the sound has been paired with a sausage, but not to a different, nonpaired sound, suggesting that its behavioral response (salivation) has changed after food conditioning. It is noteworthy that this definition bypasses both common-sensical reward notions, as the dog does not need to do anything in particular for the reward to occur (notion 1) nor is it

relevant what the dog feels (notion 2). Yet we will see that this definition is a key to neurobiological studies.

Around this time, Thorndike's (1911) Law of Effect postulated that a reward increases the frequency and intensity of a specific behavioral act that has resulted in a reward before or, as a common interpretation has it, "rewards make you come back for more." This definition comes close to the idea of instrumental conditioning, in that you get a reward for having done something well, and not automatically as with Pavlovian conditioning. It resembles Pavlov's definition of learning function, as it suggests that you will do more of the same behavior that has led previously to the rewarding outcome (positive reinforcement). Skinner pushed the definition of instrumental, or operant, conditioning further by defining rewards as reinforcers of stimulus-response links that do not require mental processes such as intention, representation of goal, or consciousness. Although the explicit antimental stance reduced the impact of his concept, the purely behaviorist approach to studying reward function allowed scientists to acquire a huge body of knowledge by studying the behavior of animals, and it paved the way to neurobiological investigations without the confounds of subjective feelings.

Reward objects for animals are primarily vegetative in nature, such as different foodstuffs and liquids with various tastes. These rewards are necessary for survival, their motivational value can be determined by controlled access, and they can be delivered in quantifiable amounts in laboratory situations. The other main vegetative reward, sex, is impossible to deliver in neurophysiological laboratory situations requiring hundreds of daily trials. Animals are also sensitive to other, nonvegetative rewards, such as touch to the skin or fur and presentation of novel objects and situations eliciting exploratory responses, but these again are difficult to parameterize for laboratory situations. Humans use a wide range of nonvegetative rewards, such as money, challenge, acclaim, visual and acoustic beauty, power, security, and many others, but these are not considered as this review considers neural mechanisms in animals.

An issue with vegetative rewards is the precise definition of the rewarding effect. Is it the seeing of an apple, its taste on the tongue, the swallowing of a bite of it, the feeling of its going down the throat, or the rise in blood sugar subsequent to its digestion that makes it a reward and has one come back for more? Which of these events constitutes the primary rewarding effect, and do different objects draw their rewarding effects from different events (Wise 2002)? In some cases, the reward may be the taste experienced when an object activates the gustatory receptors, as with saccharin, which has no nutritional effects but increases behavioral reactions. The ultimate rewarding effect of many nutrient objects may be the specific influence on vegetative parameters, such as electrolyte, glucose, and amino acid concentrations in plasma and brain. This would explain why animals avoid foods that lack such nutrients as essential amino acids (Delaney & Gelperin 1986, Hrupka et al. 1997, Rogers & Harper 1970, Wang et al. 1996). The behavioral function of some reward objects may be determined by innate mechanisms, whereas a much larger variety might be learned through experience.

Although these theories provide important insights into reward function, they tend to neglect the fact that individuals usually operate in a world with limited nutritional and mating resources, and that most resources occur with different degrees of uncertainty. The animal in the wild is not certain whether it will encounter a particular fruit or prey object at a particular moment, nor is the restaurant goer certain that her preferred chef will cook that night. To make the uncertainty of outcomes tractable was the main motive that led Blaise Pascal to develop probability theory around 1650 (see Glimcher 2003 for details). He soon realized that humans make decisions by weighing the potential outcomes by their associated probabilities and then go for the largest result. Or, mathematically speaking, they sum the products of magnitude and probability of all potential outcomes of each option and then choose the option with the highest expected value. Nearly one hundred years later, Bernoulli (1738) discovered that the utility of outcomes for decision making does not increase linearly but frequently follows a concave function, which marks the beginning of microeconomic decision theory. The theory provides quantifiable assessments of outcomes under uncertainty and has gone a long way to explain human and animal decision making, even though more recent data cast doubt on the logic in some decision situations (Kahneman & Tversky 1984).

A Call for Behavioral Theory

Primary sensory systems have dedicated physical and chemical receptors that translate environmental energy and information into neural language. Thus, the functions of primary sensory systems are governed by the laws of mechanics, optics, acoustics, and receptor binding. By contrast, there are no dedicated receptors for reward, and the information enters the brain through mechanical, gustatory, visual, and auditory receptors of the sensory systems. The functions of rewards cannot be derived entirely from the physics and chemistry of input events but are based primarily on behavioral effects, and the investigation of reward functions requires behavioral theories that can conceptualize the different effects of rewards on behavior. Thus, the exploration of neural reward mechanisms should not be based primarily on the physics and chemistry of reward objects but on specific behavioral theories that define reward functions. Animal learning theory and microeconomics are two prominent examples of such behavioral theories and constitute the basis for this review.

REWARD FUNCTIONS DEFINED BY ANIMAL LEARNING THEORY

This section will combine some of the central tenets of animal learning theories in an attempt to define a coherent framework for the investigation of neural reward mechanisms. The framework is based on the description of observable behavior and superficially resembles the behaviorist approach, although mental states

of representation and prediction are essential. Dropping the issues of subjective feelings of pleasure will allow us to do objective behavioral measurements in controlled neurophysiological experiments on animals. To induce subjective feelings of pleasure and positive emotion is a key function of rewards, although it is unclear whether the pleasure itself has a reinforcing, causal effect for behavior (i.e., I feel good because of the outcome I got and therefore will do again what produced the pleasant outcome) or is simply an epiphenomenon (i.e., my behavior gets reinforced and, in addition, I feel good because of the outcome).

Learning

Rewards induce changes in observable behavior and serve as positive reinforcers by increasing the frequency of the behavior that results in reward. In Pavlovian, or classical, conditioning, the outcome follows the conditioned stimulus (CS) irrespective of any behavioral reaction, and repeated pairing of stimuli with outcomes leads to a representation of the outcome that is evoked by the stimulus and elicits the behavioral reaction (Figure 1*a*). By contrast, instrumental, or operant, conditioning requires the subject to execute a behavioral response; without such response there will be no reward. Instrumental conditioning increases the frequency of those behaviors that are followed by reward by reinforcing stimulus-response links. Instrumental conditioning allows subjects to influence their environment and determine their rate of reward.

The behavioral reactions studied classically by Pavlov are vegetative responses governed by smooth muscle contraction and gland discharge, whereas more recent Pavlovian tasks also involve reactions of striated muscles. In the latter case, the final reward usually needs to be collected by an instrumental contraction of striated muscle, but the behavioral reaction to the CS itself, for example, anticipatory licking, is not required for the reward to occur and thus is classically conditioned. As a further emphasis on Pavlovian mechanisms, the individual stimuli in instrumental tasks that predict rewards are considered to be Pavlovian conditioned. These distinctions are helpful when trying to understand why the neural mechanisms of reward prediction reveal strong influences of Pavlovian conditioning.

Three factors govern conditioning, namely contiguity, contingency, and prediction error. Contiguity refers to the requirement of near simultaneity (Figure 1*a*). Specifically, a reward needs to follow a CS or response by an optimal interval of a few seconds, whereas rewards occurring before a stimulus or response do not contribute to learning (backward conditioning). The contingency requirement postulates that a reward needs to occur more frequently in the presence of a stimulus as compared with its absence in order to induce "excitatory" conditioning of the stimulus (Figure 1*b*); the occurrence of the CS predicts a higher incidence of reward compared with no stimulus, and the stimulus becomes a reward predictor. By contrast, if a reward occurs less frequently in the absence of a stimulus, compared with its presence, the occurrence of the stimulus predicts a lower incidence of reward, and the stimulus becomes a conditioned inhibitor, even though the contiguity

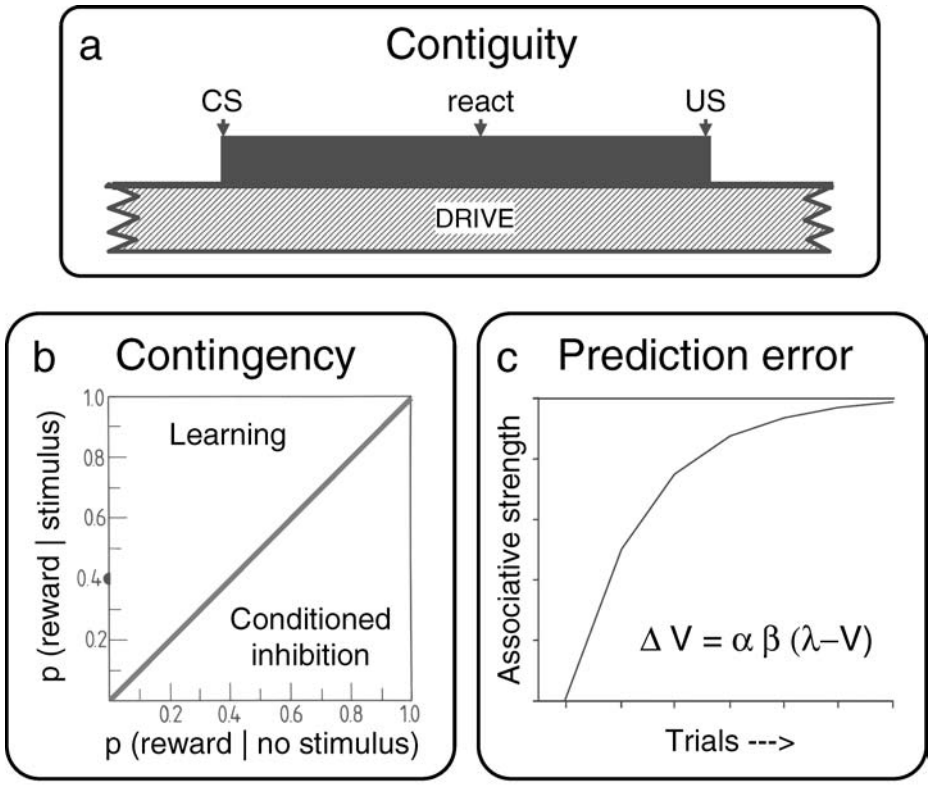


Figure 1 Basic assumptions of animal learning theory defining the behavioral functions of rewards. (*a*) Contiguity refers to the temporal proximity of a conditioned stimulus (CS), or action, and the reward. (*b*) Contingency refers to the conditional probability of reward occurring in the presence of a conditioned stimulus as opposed to its absence (modified from Dickinson 1980). (*c*) Prediction error denotes the discrepancy between an actually received reward and its prediction. Learning (ΔV, associative strength) is proportional to the prediction error (λ–V) and reaches its asymptote when the prediction error approaches zero after several learning trials. All three requirements need to be fulfilled for learning to occur. US, unconditioned stimulus.

requirement is fulfilled. The crucial role of prediction error is derived from Kamin's (1969) blocking effect, which postulates that a reward that is fully predicted does not contribute to learning, even when it occurs in a contiguous and contingent manner. This is conceptualized in the associative learning rules (Rescorla & Wagner 1972), according to which learning advances only to the extent to which a reinforcer is unpredicted and slows progressively as the reinforcer becomes more predicted (Figure 1*c*). The omission of a predicted reinforcer reduces the strength of the CS and produces extinction of behavior. So-called attentional learning rules in addition

relate the capacity to learn (associability) in certain situations to the degree of attention evoked by the CS or reward (Mackintosh 1975, Pearce & Hall 1980).

Approach Behavior

Rewards elicit two forms of behavioral reactions, approach and consumption. This is because the objects are labeled with appetitive value through innate mechanisms (primary rewards) or, in most cases, classical or instrumental conditioning, after which these objects constitute, strictly speaking, conditioned reinforcers (Wise 2002). Nutritional rewards can derive their value from hunger and thirst states, and satiation of the animal reduces the reward value and consequently the behavioral reactions.

Conditioned, reward-predicting stimuli also induce preparatory or approach behavior toward the reward. In Pavlovian conditioning, subjects automatically show nonconsummatory behavioral reactions that would otherwise occur after the primary reward and that increase the chance of consuming the reward, as if a part of the behavioral response has been transferred from the primary reward to the CS (Pavlovian response transfer).

In instrumental conditioning, a reward can become a goal for instrumental behavior if two conditions are met. The goal needs to be represented at the time the behavior is being prepared and executed. This representation should contain a prediction of the future reward together with the contingency that associates the behavioral action to the reward (Dickinson & Balleine 1994). Behavioral tests for the role of "incentive" reward-predicting mechanisms include assessing behavioral performance in extinction following devaluation of the reward by satiation or aversive conditioning in the absence of the opportunity to perform the instrumental action (Balleine & Dickinson 1998). A reduction of behavior in this situation indicates that subjects have established an internal representation of the reward that is updated when the reward changes its value. (Performing the action together with the devalued outcome would result in reduced behavior due to partial extinction, as the reduced reward value would diminish the strength of the association.) To test the role of action-reward contingencies, the frequency of "free" rewards in the absence of the action can be varied to change the strength of association between the action and the reward and thereby modulate instrumental behavior (Balleine & Dickinson 1998).

Motivational Valence

Punishers have opposite valence to rewards, induce withdrawal behavior, and act as negative reinforcers by increasing the behavior that results in decreasing the aversive outcome. Avoidance can be passive when subjects increasingly refrain from doing something that is associated with a punisher (don't do it); active avoidance involves increasing an instrumental response that is likely to reduce the impact of a punisher (get away from it). Punishers induce negative emotional states of anger, fear, and panic.

NEUROPHYSIOLOGY OF REWARD BASED ON ANIMAL LEARNING THEORY

Primary Reward

Neurons responding to liquid or food rewards are found in a number of brain structures, such as orbitofrontal, premotor and prefrontal cortex, striatum, amygdala, and dopamine neurons (Amador et al. 2000, Apicella et al. 1991, Bowman et al. 1996, Hikosaka et al. 1989, Ljungberg et al. 1992, Markowitsch & Pritzel 1976, Nakamura et al. 1992, Nishijo et al. 1988, Pratt & Mizumori 1998, Ravel et al. 1999, Shidara et al. 1998, Thorpe et al. 1983, Tremblay & Schultz 1999). Satiation of the animal reduces the reward responses in orbitofrontal cortex (Critchley & Rolls 1996) and in the secondary gustatory area of caudal orbitofrontal cortex (Rolls et al. 1989), a finding that suggests that the responses reflect the rewarding functions of the objects and not their taste. Taste responses are found in the primary gustatory area of the insula and frontal operculum and are insensitive to satiation (Rolls et al. 1988).

Contiguity

Procedures involving Pavlovian conditioning provide simple paradigms for learning and allow the experimenter to test the basic requirements of contiguity, contingency, and prediction error. Contiguity can be tested by presenting a reward 1.5–2.0 seconds after an untrained, arbitrary visual or auditory stimulus for several trials. A dopamine neuron that responds initially to a liquid or food reward acquires a response to the CS after some tens of paired CS-reward trials (Figure 2) (Mirenowicz & Schultz 1994, Waelti 2000). Responses to conditioned, reward-predicting stimuli occur in all known reward structures of the brain, including the orbitofrontal cortex, striatum, and amygdala (e.g., Hassani et al. 2001, Liu & Richmond 2000, Nishijo et al. 1988, Rolls et al. 1996, Thorpe et al. 1983, Tremblay & Schultz 1999). (Figure 2 shows that the response to the reward itself disappears in dopamine neurons, but this is not a general phenomenon with other neurons.)

Contingency

The contingency requirement postulates that in order to be involved in reward prediction, neurons should discriminate between three kinds of stimuli, namely reward-predicting CSs (conditioned exciters), after which reward occurs more frequently compared with no CS (Figure 1*b,* top left); conditioned inhibitors, after which reward occurs less frequently compared with no CS (Figure 1*b*, bottom right); and neutral stimuli that are not associated with changes in reward frequency compared with no stimulus (diagonal line in Figure 1*b*). In agreement with these postulates, dopamine neurons are activated by reward-predicting CSs, show depressions of activity following conditioned inhibitors, which may be accompanied

by small activations, and hardly respond to neutral stimuli when response generalization is excluded (Figure 3) (Tobler et al. 2003). The conditioned inhibitor in these experiments is set up by pairing the inhibitor with a reward-predicting CS while withholding the reward, which amounts to a lower probability of reward in the presence of the inhibitor compared with its absence (reward-predicting stimulus alone) and thus follows the scheme of Figure 1*b* (bottom right). Without conditioned inhibitors being tested, many studies find CS responses that distinguish between reward-predicting and neutral stimuli in all reward structures (e.g., Aosaki et al. 1994, Hollerman et al. 1998, Kawagoe et al. 1998, Kimura et al. 1984, Nishijo et al. 1988, Ravel et al. 1999, Shidara et al. 1998, Waelti et al. 2001).

Further tests assess the specificity of information contained in CS responses. In the typical behavioral tasks used in monkey experiments, the CS may contain several different stimulus components, namely spatial position; visual object features such as color, form, and spatial frequency; and motivational features such as reward prediction. It would be necessary to establish through behavioral testing which of these features is particularly effective in evoking a neural response. For example, neurons in the orbitofrontal cortex discriminate between different CSs on the basis of their prediction of different food and liquid rewards (Figure 4) (Critchley & Rolls 1996, Tremblay & Schultz 1999). By contrast, these neurons are less sensitive to the visual object features of the same CSs, and they rarely code their spatial position, although neurons in other parts of frontal cortex are particularly tuned to these nonreward parameters (Rao et al. 1997). CS responses that are primarily sensitive to the reward features are found also in the amygdala (Nishijo et al. 1988) and striatum (Hassani et al. 2001). These data suggest that individual neurons in these structures can extract the reward components from the multidimensional stimuli used in these experiments as well as in everyday life.

Reward neurons should distinguish rewards from punishers. Different neurons in orbitofrontal cortex respond to rewarding and aversive liquids (Thorpe et al. 1983). Dopamine neurons are activated preferentially by rewards and reward-predicting stimuli but are only rarely activated by aversive air puffs and saline (Mirenowicz & Schultz 1996). In anesthetized animals, dopamine neurons show depressions following painful stimuli (Schultz & Romo 1987, Ungless et al. 2004). Nucleus accumbens neurons in rats show differential activating or depressing responses to CSs predicting rewarding sucrose versus aversive quinine solutions in a Pavlovian task (Roitman et al. 2005). By contrast, the group of tonically active neurons of the striatum responds to both rewards and aversive air puffs, but not to neutral stimuli (Ravel et al. 1999). They seem to be sensitive to reinforcers in general, without specifying their valence. Alternatively, their responses might reflect the higher attention-inducing effects of reinforcers compared with neutral stimuli.

The omission of reward following a CS moves the contingency toward the diagonal line in Figure 1*b* and leads to extinction of learned behavior. By analogy, the withholding of reward reduces the activation of dopamine neurons by CSs within several tens of trials (Figure 5) (Tobler at al. 2003).

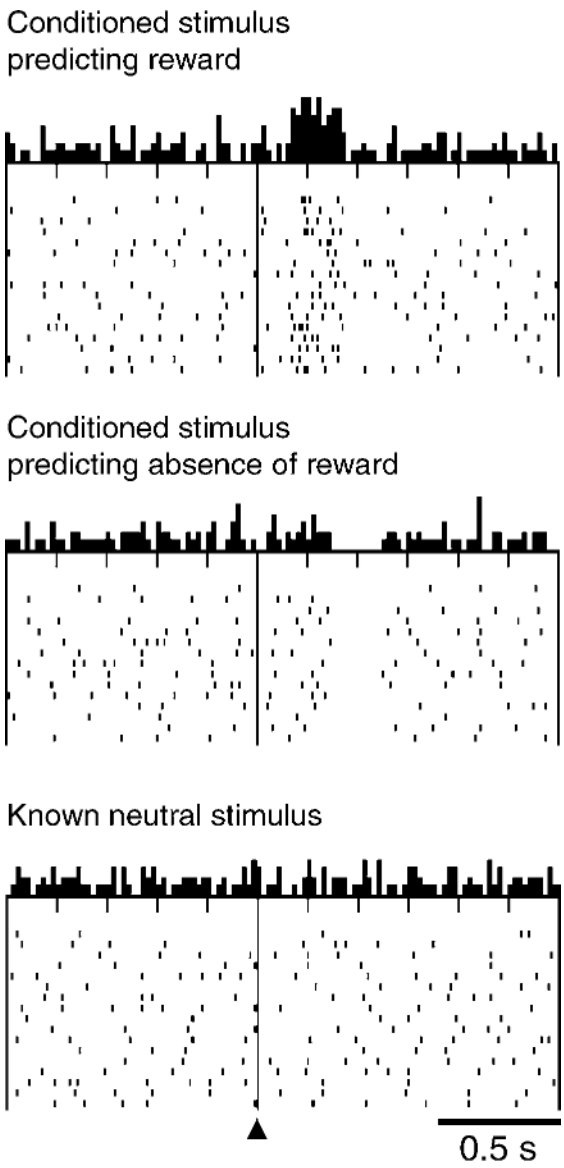
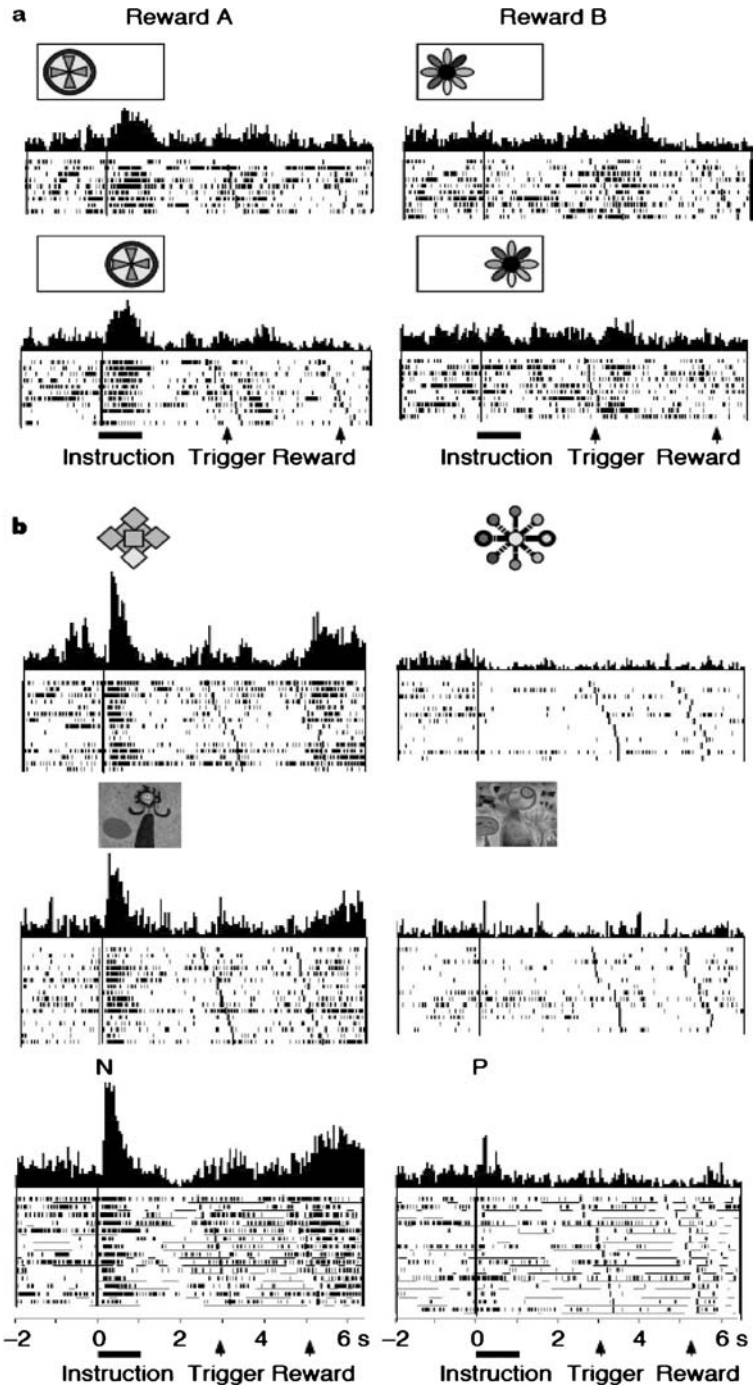


Figure 3 Testing the contingency requirement for associative learning: responses of a single dopamine neuron to three types of stimuli. (*Top*) Activating response to a reward-predicting stimulus (higher occurrence of reward in the presence as opposed to absence of stimulus). (*Middle*) Depressant response to a different stimulus predicting the absence of reward (lower occurrence of reward in the presence as opposed to absence of stimulus). (*Bottom*) Neutral stimulus (no change in reward occurrence after stimulus). Vertical line and arrow indicate time of stimulus.



Prediction Error

Just as with behavioral learning, the acquisition of neuronal responses to reward-predicting CSs should depend on prediction errors. In the prediction error–defining blocking paradigm, dopamine neurons acquire a response to a CS only when the CS is associated with an unpredicted reward, but not when the CS is paired with a reward that is already predicted by another CS and the occurrence of the reward does not generate a prediction error (Figure 6) (Waelti et al. 2001). The neurons fail to learn to respond to reward predictors despite the fact that contiguity and contingency requirements for excitatory learning are fulfilled. These data demonstrate the crucial importance of prediction errors for associative neural learning and suggest that learning at the single-neuron level may follow similar rules as those for behavioral learning. This suggests that some behavioral learning functions may be carried by populations of single neurons.

Neurons may not only be sensitive to prediction errors during learning, but they may also emit a prediction error signal. Dopamine neurons, and some neurons in orbitofrontal cortex, show reward activations only when the reward occurs unpredictably and fail to respond to well-predicted rewards, and their activity is depressed when the predicted reward fails to occur (Figure 7) (Mirenowicz & Schultz 1994, Tremblay & Schultz 2000a). This result has prompted the notion that dopamine neurons emit a positive signal (activation) when an appetitive event is better than predicted, no signal (no change in activity) when an appetitive event occurs as predicted, and a negative signal (decreased activity) when an appetitive event is worse than predicted (Schultz et al. 1997). In contrast to this bidirectional error signal, some neurons in the prefrontal, anterior, and posterior cingulate cortex show a unidirectional error signal upon activation when a reward fails to occur because of a behavioral error of the animal (Ito et al. 2003, McCoy et al. 2003, Watanabe 1989; for review of neural prediction errors, see Schultz & Dickinson 2000).

More stringent tests for the neural coding of prediction errors include formal paradigms of animal learning theory in which prediction errors occur in specific situations. In the blocking paradigm, the blocked CS does not predict a reward. Accordingly, the absence of a reward following that stimulus does not produce a prediction error nor a response in dopamine neurons, and the delivery of a reward does produce a positive prediction error and a dopamine response (Figure 8*a*; left) (Waelti et al. 2001). By contrast, after a well-trained,

Figure 4 Reward discrimination in orbitofrontal cortex. (*a*) A neuron responding to the instruction cue predicting grenadine juice (*left*) but not apple juice (*right*), irrespective of the left or right position of the cue in front of the animal. (*b*) A different neuron responding to the cue predicting grape juice (*left*) but not orange juice (*right*), irrespective of the picture object predicting the juice. From Tremblay & Schultz 1999, ¢ Nature MacMillan Publishers.

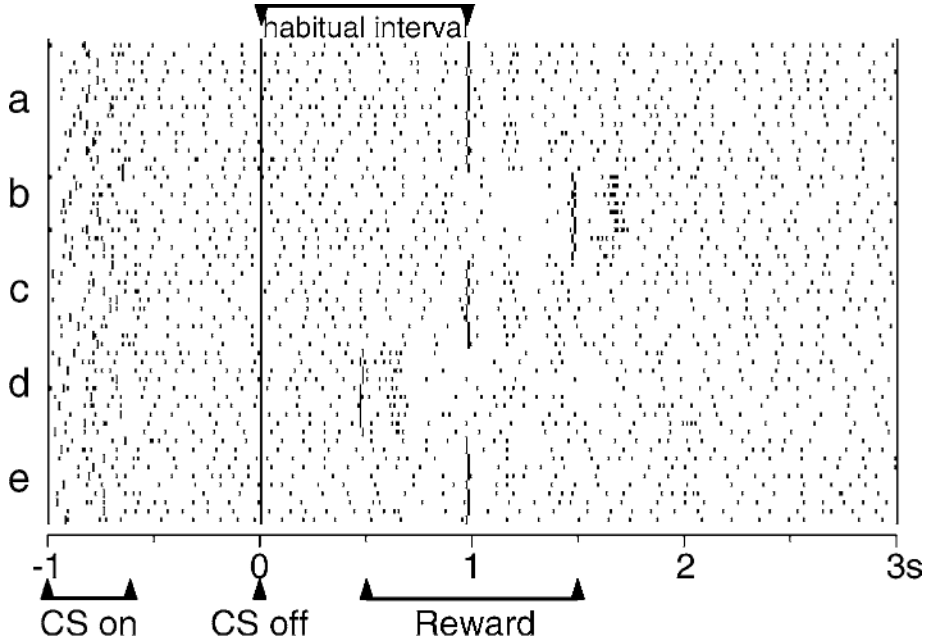


Figure 7 Dopamine response codes temporal reward prediction error. (*a*, *c*, *e*) No response to reward delivered at habitual time. (*b*) Delay in reward induces depression at previous time of reward, and activation at new reward time. (*d*) Precocious reward delivery induces activation at new reward time, but no depression at previous reward time. Trial sequence is from top to bottom. Data from Hollerman & Schultz (1998). CS, conditioned stimulus.

reward-predicting CS, reward omission produces a negative prediction error and a depressant neural response, and reward delivery does not lead to a prediction error or a response in the same dopamine neuron (Figure 8*a*; right). In a conditioned inhibition paradigm, the conditioned inhibitor predicts the absence of reward, and the absence of reward after this stimulus does not produce a prediction error or a response in dopamine neurons, even when another, otherwise reward-predicting stimulus is added (Figure 8*b*) (Tobler at al. 2003). By contrast, the occurrence of reward after an inhibitor produces an enhanced prediction error, as the prediction error represents the difference between the actual reward and the negative prediction from the inhibitor, and the dopamine neuron shows a strong response (Figure 8*b*; bottom). Taken together, these data suggest that dopamine neurons show bidirectional coding of reward prediction errors, following the equation

Dopamine response D Reward occurred D Reward predicted.

This equation may constitute a neural equivalent for the prediction error term of (λ–V) of the Rescorla-Wagner learning rule. With these characteristics, the

bidirectional dopamine error response would constitute an ideal teaching signal for neural plasticity.

The neural prediction error signal provides an additional means to investigate the kinds of information contained in the representations evoked by CSs. Time apparently plays a major role in behavioral learning, as demonstrated by the unblocking effects of temporal variations of reinforcement (Dickinson et al. 1976). Figure 7 shows that the prediction acting on dopamine neurons concerns the exact time of reward occurrence. Temporal deviations induce a depression when the reward fails to occur at the predicted time (time-sensitive reward omission response), and an activation when the reward occurs at a moment other than predicted (Hollerman & Schultz 1998). This time sensitivity also explains why neural prediction errors occur at all in the laboratory in which animals know that they will receive ample quantities of reward but without knowing when exactly the reward will occur. Another form of time representation is revealed by tests in which the probability of receiving a reward after the last reward increases over consecutive trials. Thus, the animal's reward prediction should increase after each unrewarded trial, the positive prediction error with reward should decrease, and the negative prediction error with reward omission should increase. In line with this reasoning, dopamine neurons show progressively decreasing activations to reward delivery as the number of trials since the last reward increases, and increasing depressions in unrewarded trials (Figure 9) (Nakahara et al. 2004). The result suggests that, for the neurons, the reward prediction in the CS increases after every unrewarded trial, due to the temporal profile of the task evoked by the CS, and contradicts an assumption from temporal difference reinforcement modeling that the prediction error of the preceding unrewarded trial would reduce the current reward prediction in the CS, in which case the neural prediction error responses should increase, which is the opposite to what is actually observed (although the authors attribute the temporal conditioning to the context and have the CS conform to the temporal difference model). The results from the two experiments demonstrate that dopamine neurons are sensitive to different aspects of temporal information evoked by reward-predicting CSs and demonstrate how experiments based on specific behavioral concepts, namely prediction error, reveal important characteristics of neural coding.

The uncertainty of reward is a major factor for generating the attention that determines learning according to the associability learning rules (Mackintosh 1975, Pearce & Hall 1980). When varying the probability of reward in individual trials from 0 to 1, reward becomes most uncertain at $p = 0.5$, as it is most unclear whether or not a reward will occur. (Common perception might say that reward is even more uncertain at $p = 0.25$; however, at this low probability, it is nearly certain that reward will not occur.) Dopamine neurons show a slowly increasing activation between the CS and reward that is maximal at $p = 0.5$ (Fiorillo et al. 2003). This response may constitute an explicit uncertainty signal and is different in time and occurrence from the prediction error response. The response might contribute to a teaching signal in situations defined by the associability learning rules.

Approach Behavior and Goal Directedness

Many behavioral tasks in the laboratory involve more than a CS and a reward and comprise instrumental ocular or skeletal reactions, mnemonic delays between instruction cues and behavioral reactions, and delays between behavioral reactions and rewards during which animals can expect the reward.

Appropriately conditioned stimuli can evoke specific expectations of reward, and phasic neural responses to these CSs may reflect the process of evocation (see above). Once the representations have been evoked, their content can influence the behavior during some time. Neurons in a number of brain structures show sustained activations after an initial CS has occurred. The activations arise usually during specific epochs of well-differentiated instrumental tasks, such as during movement preparation (Figure 10*a*) and immediately preceding the reward (Figure 10*b*), whereas few activations last during the entire period between CS and reward. The activations differentiate between reward and no reward, between different kinds of liquid and food reward, and between different magnitudes of reward. They occur in all trial types in which reward is expected, irrespective of the type of behavioral action (Figure 10). Thus, the activations appear to represent reward expectations. They are found in the striatum (caudate, putamen, ventral

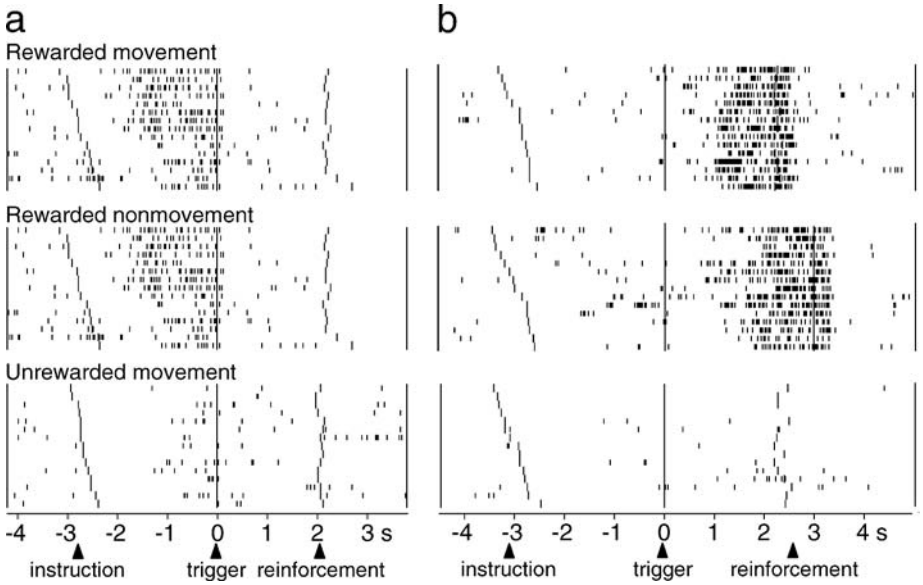


Figure 10 Reward expectation in the striatum. (*a*) Activation in a caudate neuron preceding the stimulus that triggers the movement or nonmovement reaction in both rewarded trial types irrespective of movement, but not in unrewarded movement trials. (*b*) Activation in a putamen neuron preceding the delivery of liquid reward in both rewarded trial types, but not before the reinforcing sound in unrewarded movement trials. Data from Hollerman et al. (1998).

striatum), amygdala, orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate, and supplementary eye field (Amador et al. 2000, Apicella et al. 1992, Cromwell & Schultz 2003, Hikosaka et al. 1989, Hollerman et al. 1998, Pratt & Mizumori 2001, Schoenbaum et al. 1998, Schultz et al. 1992, Shidara & Richmond 2002, Tremblay & Schultz 1999, 2000a, Watanabe 1996, Watanabe et al. 2002). Reward expectation-related activity in orbitofrontal cortex and amygdala develops as the reward becomes predictable during learning (Schoenbaum et al. 1999). In learning episodes with pre-existing reward expectations, orbitofrontal and striatal activations occur initially in all situations but adapt to the currently valid expectations, for example when novel stimuli come to indicate rewarded versus unrewarded trials. The neural changes occur in parallel with the animal's behavioral differentiation (Tremblay et al. 1998, Tremblay & Schultz 2000b).

In some neurons, the differential reward expectation-related activity discriminates in addition between different behavioral responses, such as eye and limb movements toward different spatial targets and movement versus nonmovement reactions (Figure 11). Such neurons are found in the dorsolateral prefrontal cortex (Kobayashi et al. 2002, Matsumoto et al. 2003, Watanabe 1996) and striatum

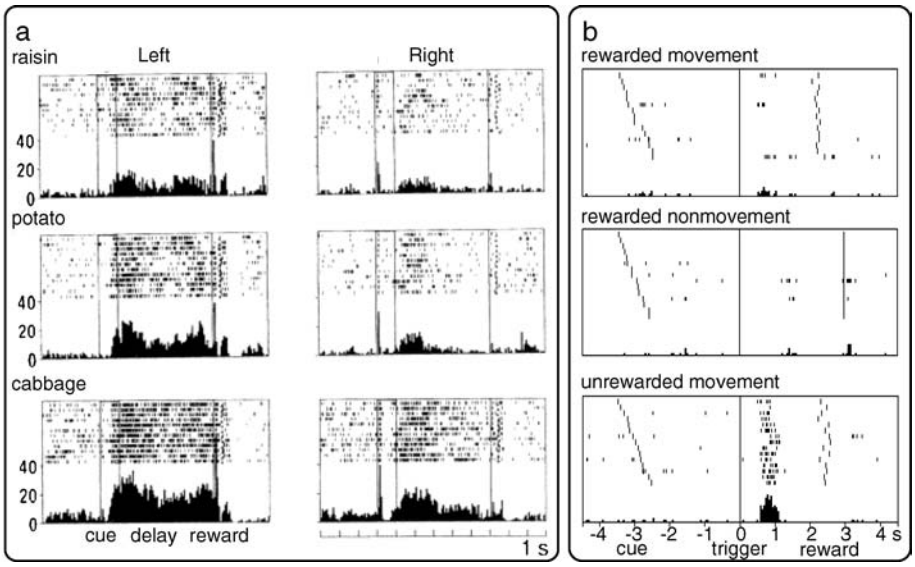


Figure 11 Potential neural mechanisms underlying goal-directed behavior. (*a*) Delay activity of a neuron in primate prefrontal cortex that encodes, while the movement is being prepared, both the behavioral reaction (left versus right targets) and the kind of outcome obtained for performing the action. From Watanabe (1996), © Nature MacMillan Publishers. (*b*) Response of a caudate neuron to the movement-triggering stimulus exclusively in unrewarded trials, thus coding both the behavioral reaction being executed and the anticipated outcome of the reaction. Data from Hollerman et al. (1998).

(Cromwell & Schultz 2003, Hassani et al. 2001, Hollerman et al. 1998, Kawagoe et al. 1998). The activations occur during task epochs related to the preparation and execution of the movement that is performed in order to obtain the reward. They do not simply represent outcome expectation, as they differentiate between different behavioral reactions despite the same outcome (Figure 11*a*, left versus right; Figure 11*b*, movement versus nonmovement), and they do not simply reflect different behavioral reactions, as they differentiate between the expected outcomes (Figure 11*a*,*b*, top versus bottom). Or, expressed in another way, the neurons show differential, behavior-related activations that depend on the outcome of the trial, namely reward or no reward and different kinds and magnitudes of reward. The differential nature of the activations develops during learning while the different reward expectations are being acquired, similar to simple reward expectation-related activity (Tremblay et al. 1998).

It is known that rewards have strong attention-inducing functions, and reward-related activity in parietal association cortex might simply reflect the known involvement of these areas in attention (Maunsell 2004). It is often tedious to disentangle attention from reward, but one viable solution would be to test neurons for specificity for reinforcers with opposing valence while keeping the levels of reinforcement strength similar for rewards and punishers. The results of such tests suggest that dopamine neurons and some neurons in orbitofrontal cortex discriminate between rewards and aversive events and thus report reward-related but not attention-related stimulus components (Mirenowicz & Schultz 1996, Thorpe et al. 1983). Also, neurons showing increasing activations with decreasing reward value or magnitude are unlikely to reflect the attention associated with stronger rewards. Such inversely related neurons exist in the striatum and orbitofrontal cortex (Hassani et al. 2001, Hollerman et al. 1998, Kawagoe et al. 1998, Watanabe 1996).

General learning theory suggests that Pavlovian associations of reward-predicting stimuli in instrumental tasks relate either to explicit CSs or to contexts. The neural correlates of behavioral associations with explicit stimuli may not only involve the phasic responses to CSs described above but also activations at other task epochs. Further neural correlates of Pavlovian conditioning may consist of the sustained activations that occur during the different task periods preceding movements or rewards (Figure 10), which are only sensitive to reward parameters and not to the types of behavioral reactions necessary to obtain the rewards.

Theories of goal-directed instrumental behavior postulate that in order to consider rewards as goals of behavior, there should be (*a*) an expectation of the outcome at the time of the behavior that leads to the reward, and (*b*) a representation of the contingency between the instrumental action and the outcome (Dickinson & Balleine 1994). The sustained, reward-discriminating activations may constitute a neural mechanism for simple reward expectation, as they reflect the expected reward without differentiating between behavioral reactions (Figure 10). However, these activations are not fully sufficient correlates for goal-directed behavior, as the reward expectation is not necessarily related to the specific action that results in the goal being attained; rather, it might refer to an unrelated reward

that occurs in parallel and irrespective of the action. Such a reward would not constitute a goal of the action, and the reward-expecting activation might simply reflect the upcoming reward without being involved in any goal mechanism. By contrast, reward-expecting activations might fulfill the second, more stringent criterion if they are also specific for the action necessary to obtain the reward. These reward-expecting activations differentiate between different behavioral acts and arise only under the condition that the behavior leading to the reward is being prepared or executed (Figure 11). Mechanistically speaking, the observed neural activations may be the result of convergent neural coding of reward and behavior, but from a theoretical point, the activations could represent evidence for neural correlates of goal-directed mechanisms. To distinguish between the two possibilities, it would be helpful to test explicitly the contingency requirement by varying the probabilities of reward in the presence versus absence of behavioral reactions. Further tests could employ reward devaluations to distinguish between goal-directed and habit mechanisms, as the relatively more simple habits might also rely on combined neural mechanisms of expected reward and behavioral action but lack the more flexible representations of reward that are the hallmark of goal mechanisms.

REWARD FUNCTIONS DEFINED BY MICROECONOMIC UTILITY THEORY

How can we compare apples and pears? We need a numerical scale in order to assess the influence of different rewards on behavior. A good way to quantify the value of individual rewards is to compare them in choice behavior. Given two options, I would choose the one that at this moment has the higher value for me. Give me the choice between a one-dollar bill and an apple, and you will see which one I prefer and thus my action will tell you whether the value of the apple for me is higher or lower or similar compared with one dollar. To be able to put a quantifiable, numerical value onto every reward, even when the value is short-lived, has enormous advantages for getting reward-related behavior under experimental control.

To obtain a more complete picture, we need to take into account the uncertainty with which rewards frequently occur. One possibility would be to weigh the value of individual rewards with the probability with which they occur, an approach taken by Pascal ca. 1650. The sum of the products of each potential reward and its probability defines the expected value (EV) of the probability distribution and thus the theoretically expected payoff of an option, according to

$$EV = \sum_i (p_i \times x_i);\ i = 1, n;\ n = \text{number of rewards.}$$

With increasing numbers of trials, the measured mean of the actually occurring distribution will approach the expected value. Pascal conjectured that human choice behavior could be approximated by this procedure.

Despite its advantages, expected value theory has limits when comparing very small with very large rewards or when comparing values at different start positions. Rather than following physical sizes of reward value in a linear fashion, human choice behavior in many instances increases more slowly as the values get higher, and the term of utility, or in some cases prospect, replaces the term of value when the impact of rewards on choices is assessed (Bernoulli 1738, Kahneman & Tversky 1984, Savage 1954, von Neumann & Morgenstern 1944). The utility function can be modeled by various equations (for detailed descriptions, see Gintis 2000, Huang & Litzenberger 1988), such as

1. The logarithmic utility function, $u(x) = \ln(x)$, yields a concave curve similar to the Weber (1850) function of psychophysics.
2. The power utility function, $u(x) = x^a$. With $a \in (0,1)$, and often $a \in [0.66, 0.75]$, the function is concave and resembles the power law of psychophysics (Stevens 1957). By contrast, $a = 1.0$ produces a linear function in which utility (value) = value. With $a > 1$, the curve becomes convex and increases faster toward higher values.
3. The exponential utility function, $u(x) = 1 - e^{-bx}$, produces a concave function for $b \in (0,1)$.
4. With the weighted reward value being expressed as utility, the expected value of a gamble becomes the expected utility (EU) according to

$$EU = \sum_i (p_i \cdot u(x_i)); i = 1, n; n = \text{number of rewards.}$$

Assessing the expected utility allows comparisons between gambles that have several outcomes with different values occurring at different probabilities. Note that a gamble with a single reward occurring at a $p < 1$ actually has two outcomes, the reward occurring with p and the nonreward with $(1 - p)$. A gamble with only one reward at $p = 1.0$ is called a safe option. Risk refers simply to known probabilities of < 1.0 and does not necessarily involve loss. Risky gambles have known probabilities; ambiguous gambles have probabilities unknown to the agent.

The shape of the utility function allows us to deal with the influence of uncertainty on decision-making. Let us assume an agent whose decision making is characterized by a concave utility function, as shown in Figure 12, who performs in a gamble with two outcomes of values 1 and 9 at $p = 0.5$ each (either the lower or the higher outcome will occur, with equal probability). The EV of the gamble is 5 (vertical dotted line), and the utility u(EV) (horizontal dotted line) lies between u(1) and u(9) (horizontal lines). Interestingly, u(EV) lies closer to u(9) than to u(1), suggesting that the agent foregoes more utility when the gamble produces u(1) than she wins with u(9) over u(EV). Given that outcomes 1 and 9 occur with the same frequency, this agent would profit more from a safe reward at EV, with u(EV), over the gamble. She should be risk averse. Thus, a concave utility function suggests risk aversion, whereas a convex function, in which an

agent foregoes less reward than she wins, suggests risk seeking. Different agents with different attitudes toward risk have differently shaped utility functions.

A direct measure of the influence of uncertainty is obtained by considering the difference between u(EV) and the EU of the gamble. The EU in the case of equal probabilities is the mean of u(1) and u(9), as marked by EU(1–9), which is considerably lower than u(EV) and thus indicates the loss in utility due to risk. By comparison, the gamble of 4 and 6 involves a smaller range of reward magnitudes and thus less risk and less loss due to uncertainty, as seen by comparing the vertical bars associated with EU(4–6) and EU(1–9). This graphical analysis suggests that value and uncertainty of outcome can be considered as separable measures.

A separation of value and uncertainty as components of utility can be achieved mathematically by using, for example, the negative exponential utility function often employed in financial mathematics. Using the exponential utility function for EU results in

$$EU = \sum_i (p_i \cdot e^{-b x_i}),$$

which can be developed by the Laplace transform into

$$EU = e^{-b(EV - b/2 \cdot var)},$$

where EV is expected value, var is variance, and the probability distribution pi is Gaussian. Thus, EU is expressed as f(EV, variance). This procedure uses variance as a measure of uncertainty. Another measure of uncertainty is the entropy of information theory, which might be appropriate to use when dealing with information processing in neural systems, but entropy is not commonly employed for describing decision making in microeconomics.

Taken together, microeconomic utility theory has defined basic reward parameters, such as magnitude, probability, expected value, expected utility, and variance, that can be used for neurobiological experiments searching for neural correlates of decision making under uncertainty.

NEUROPHYSIOLOGY OF REWARD BASED ON ECONOMIC THEORY

Magnitude

The easiest quantifiable measure of reward for animals is the volume of juice, which animals can discriminate in submilliliter quantities (Tobler et al. 2005). Neurons show increasing responses to reward-predicting CSs with higher volumes of reward in a number of reward structures, such as the striatum (Cromwell & Schultz 2003) (Figure 13*a*), dorsolateral and orbital prefrontal cortex (Leon & Shadlen 1999, Roesch & Olson 2004, Wallis & Miller 2003), parietal and posterior cingulate cortex (McCoy et al. 2003, Musallam et al. 2004, Platt & Glimcher 1999),

and dopamine neurons (Satoh et al. 2003, Tobler et al. 2005). Similar reward magnitude–discriminating activations are found in these structures in relation to other task events, before and after reward delivery. Many of these studies also report decreasing responses with increasing reward magnitude (Figure 13*b*), although not with dopamine neurons. The decreasing responses are likely to reflect true magnitude discrimination rather than simply the attention induced by rewards, which should increase with increasing magnitude.

Recent considerations cast doubt on the nature of some of the reward magnitude–discriminating, behavior-related activations, in particular in structures involved in motor and attentional processes, such as the premotor cortex, frontal eye fields, supplementary eye fields, parietal association cortex, and striatum. Some reward-related differences in movement-related activations might reflect the differences in movements elicited by different reward magnitudes (Lauwereyns et al. 2002, Roesch & Olson 2004). A larger reward might make the animal move faster, and increased neural activity in premotor cortex with larger reward might reflect the higher movement speed. Although a useful explanation for motor structures, the issue might be more difficult to resolve for areas more remote from motor output, such as prefrontal cortex, parietal cortex, and caudate nucleus. It would be helpful to correlate reward magnitude–discriminating activity in single neurons with movement parameters, such as reaction time and movement speed, and, separately, with reward parameters, and see where higher correlations are obtained. However, the usually measured movement parameters may not be sensitive enough to make these distinctions when neural activity varies relatively little with reward magnitude. On the other hand, inverse relationships, such as higher neural activity for slower movements associated with smaller rewards, would argue against a primarily motor origin of reward-related differences, as relatively few neurons show higher activity with slower movements.

Probability

Simple tests for reward probability involve CSs that differentially predict the probability with which a reward, as opposed to no reward, will be delivered for trial completion in Pavlovian or instrumental tasks. Dopamine neurons show increasing phasic responses to CSs that predict reward with increasing probability (Fiorillo et al. 2003, Morris et al. 2004). Similar increases in task-related activity occur in parietal cortex and globus pallidus during memory and movement-related task periods (Arkadir et al. 2004, Musallam et al. 2004, Platt & Glimcher 1999). However, reward-responsive tonically active neurons in the striatum do not appear to be sensitive to reward probability (Morris et al. 2004), indicating that not all neurons sensitive to reward may code its value in terms of probability. In a decision-making situation with varying reward probabilities, parietal neurons track the recently experienced reward value, indicating a memory process that would provide important input information for decision making (Sugrue et al. 2004).

Expected Value

Parietal neurons show increasing task-related activations with both the magnitude and probability of reward that do not seem to distinguish between the two components of expected value (Musallam et al. 2004). When the two value parameters are tested separately and in combination, dopamine neurons show monotonically increasing responses to CSs that predict increasing value (Tobler et al. 2005). The neurons fail to distinguish between magnitude and probability and seem to code their product (Figure 14*a*). However, the neural noise inherent in the stimulus-response relationships makes it difficult to determine exactly whether dopamine neurons encode expected value or expected utility. In either case, it appears as if neural responses show a good relationship to theoretical notions of outcome value that form a basis for decision making.

Uncertainty

Graphical analysis and application of the Laplace transform on the exponential utility function would permit experimenters to separate the components of expected value and utility from the uncertainty inherent in probabilistic gambles. Would the

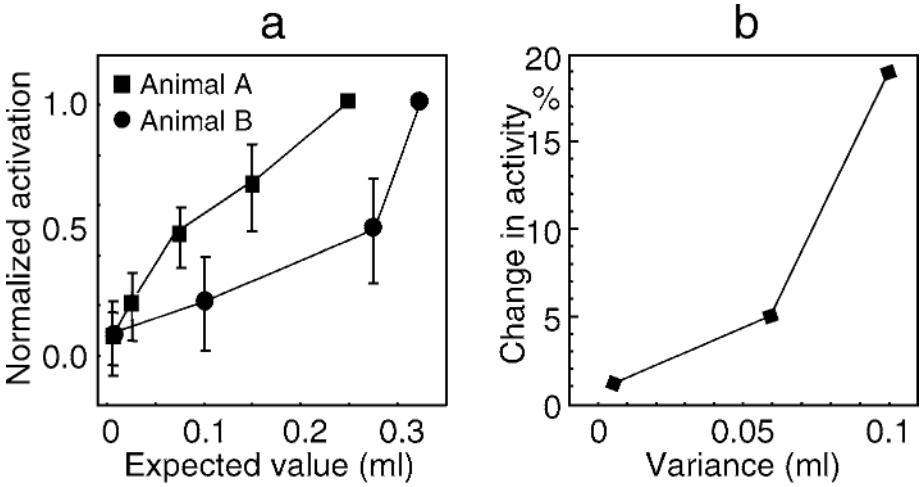


Figure 14 Separate coding of reward value and uncertainty in dopamine neurons. (*a*) Phasic response to conditioned, reward-predicting stimuli scales with increasing expected value (EV, summed magnitude □ probability). Data points represent median responses normalized to response to highest EV (animal A, 57 neurons; animal B, 53 neurons). Data from Tobler et al. (2005). (*b*) Sustained activation during conditioned stimulus–reward interval scales with increasing uncertainty, as measured by variance. Two reward magnitudes are delivered at p D 0.5 each (0.05–0.15, 0.15–0.5 ml, 0.05–0.5 ml). Ordinate shows medians of changes above background activity from 53 neurons. Note that the entropy stays 1 bit for all three probability distributions. Data from Fiorillo et al. (2003).

brain be able to produce an explicit signal that reflects the level of uncertainty, similar to producing a reward signal? For both reward and uncertainty, there are no specialized sensory receptors. A proportion of dopamine neurons show a sustained activation during the CS-reward interval when tested with CSs that predict reward at increasing probabilities, as opposed to no reward. The activation is highest for reward at p = 0.5 and progressively lower for probabilities further away from p = 0.5 in either direction (Fiorillo et al. 2003). The activation does not occur when reward is substituted by a visual stimulus. The activations appear to follow common measures of uncertainty, such as statistical variance and entropy, both of which are maximal at p = 0.5. Most of the dopamine neurons signaling reward uncertainty also show phasic responses to reward-predicting CSs that encode expected value, and the two responses coding different reward terms are not correlated with each other. When in a refined experiment two different reward magnitudes alternate randomly (each at p = 0.5), dopamine neurons show the highest sustained activation when the reward range is largest, indicating a relationship to the statistical variance and thus to the uncertainty of the reward (Figure 14*b*). In a somewhat comparable experiment, neurons in posterior cingulate cortex show increased task-related activations as animals choose among rewards with larger variance compared with safe options (McCoy & Platt 2003). Although only a beginning, these data suggest that indeed the brain may produce an uncertainty signal about rewards that could provide essential information when making decisions under uncertainty. The data on dopamine neurons suggest that the brain may code the expected value separately from the uncertainty, just as the two terms constitute separable components of expected utility when applying the Laplace transform on the exponential utility function.

CONCLUSIONS

It is intuitively simple to understand that the use of well-established behavioral theories can only be beneficial when working with mechanisms underlying behavioral reactions. Indeed, these theories can very well define the different functions of rewards on behavior. It is then a small step on firm ground to base the investigation of neural mechanisms underlying the different reward functions onto the phenomena characterized by these theories. Although each theory has its own particular emphasis, they deal with the same kinds of outcome events of behavior, and it is more confirmation than surprise to see that many neural reward mechanisms can be commonly based on, and understood with, several theories. For the experimenter, the use of different theories provides good explanations for an interesting spectrum of reward functions that may not be so easily accessible by using only a single theory. For example, it seems that uncertainty plays a larger role in parts of microeconomic theory than in learning theory, and the investigation of neural mechanisms of uncertainty in outcomes of behavior can rely on several hundred years of thoughts about decision making (Pascal 1650 in Glimcher 2003, Bernoulli 1738).

ACKNOWLEDGMENTS

This article is based on lectures delivered at a Society for Neuroscience Meeting in October 2004 in San Diego and on a Max-Planck Symposium in January 2005 in Frankfurt, Germany. The author wishes to thank Drs. Anthony Dickinson and Peter Bossaerts for illuminating discussions on behavioral theories. Our work was supported by grants from the Wellcome Trust, Swiss National Science Foundation, Human Frontiers, and European Community.

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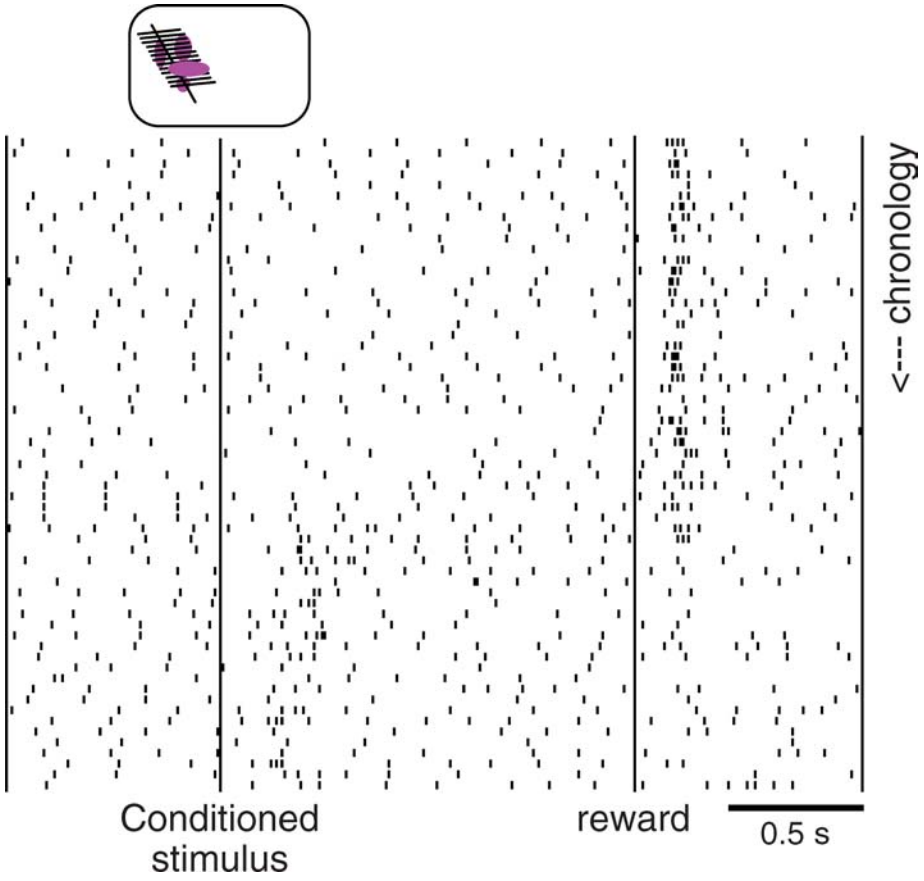

Figure 2 Testing the contiguity requirement for associative learning: acquisition of neural response in a single dopamine neuron during a full learning episode. Each line of dots represents a trial, each dot represents the time of the discharge of the dopamine neuron, the vertical lines indicate the time of the stimulus and juice reward, and the picture above the raster shows the visual conditioned stimulus presented to the monkey on a computer screen. Chronology of trials is from top to bottom. The top trial shows the activity of the neuron while the animal saw the stimulus for the first time in its life, whereas it had previous experience with the liquid reward. Data from Waelti (2000).

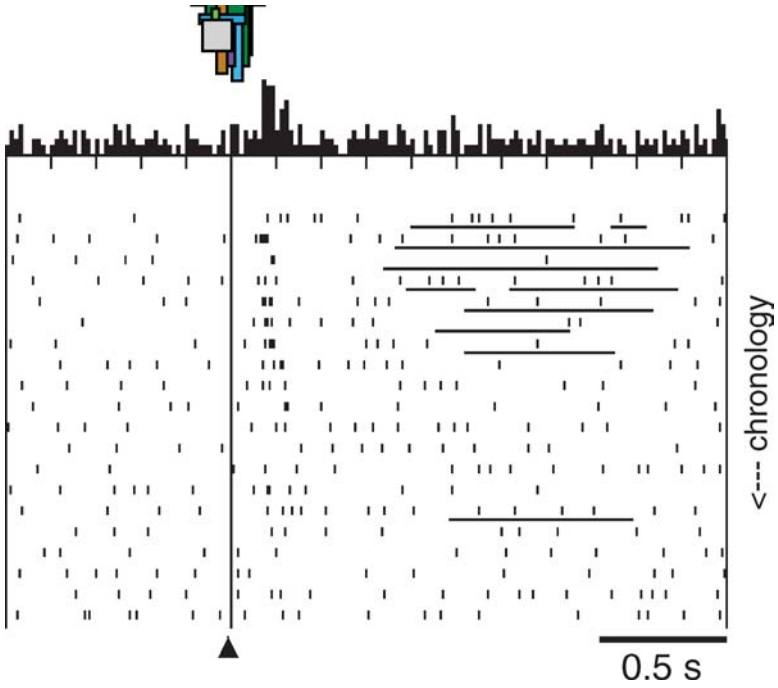

Figure 5 Loss of response in dopamine neuron to the conditioned stimulus following withholding of reward. This manipulation violates the contiguity requirement (co-occurrence of reward and stimulus) and produces a negative prediction error that brings down the associative strength of the stimulus. The contingency moves toward the neutral situation. Data from Tobler et al. (2003).

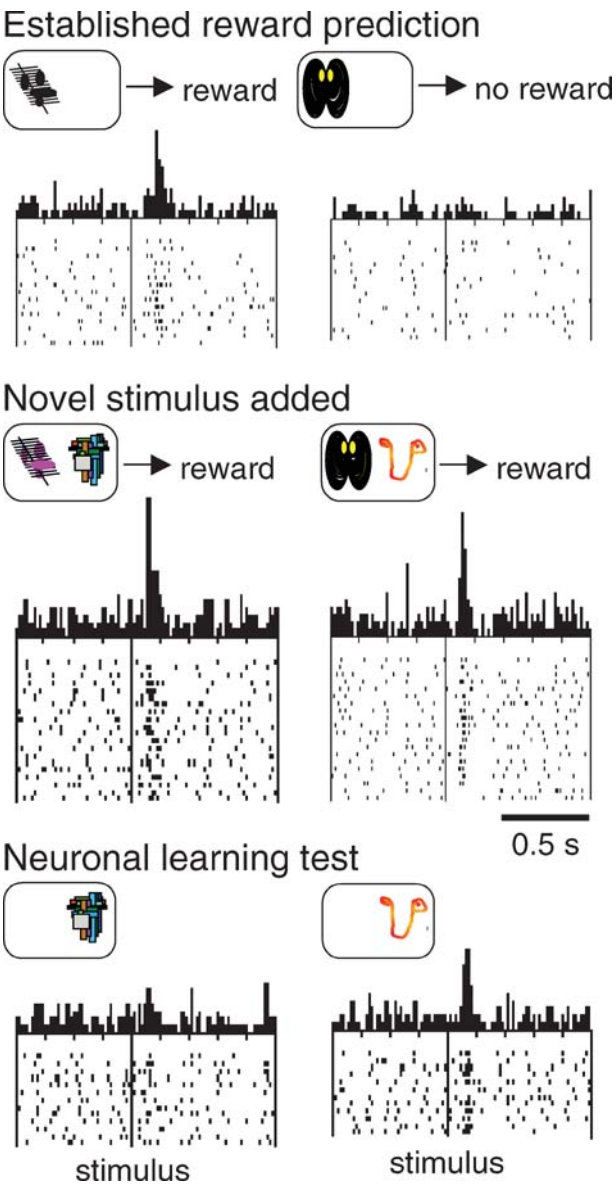

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Figure 6 Acquisition of dopamine response to reward-predicting stimulus is governed by prediction error. Neural learning is blocked when the reward is predicted by another stimulus (left) but is intact in the same neuron when reward is unpredicted in control trials with different stimuli (right). The neuron has the capacity to respond to reward-predicting stimuli (top left) and discriminates against unrewarded stimuli (top right). The addition of a second stimulus results in maintenance and acquisition of response, respectively (middle). Testing the added stimulus reveals absence of learning when the reward is already predicted by a previously conditioned stimulus (bottom left). Data from Waelti et al. (2001).

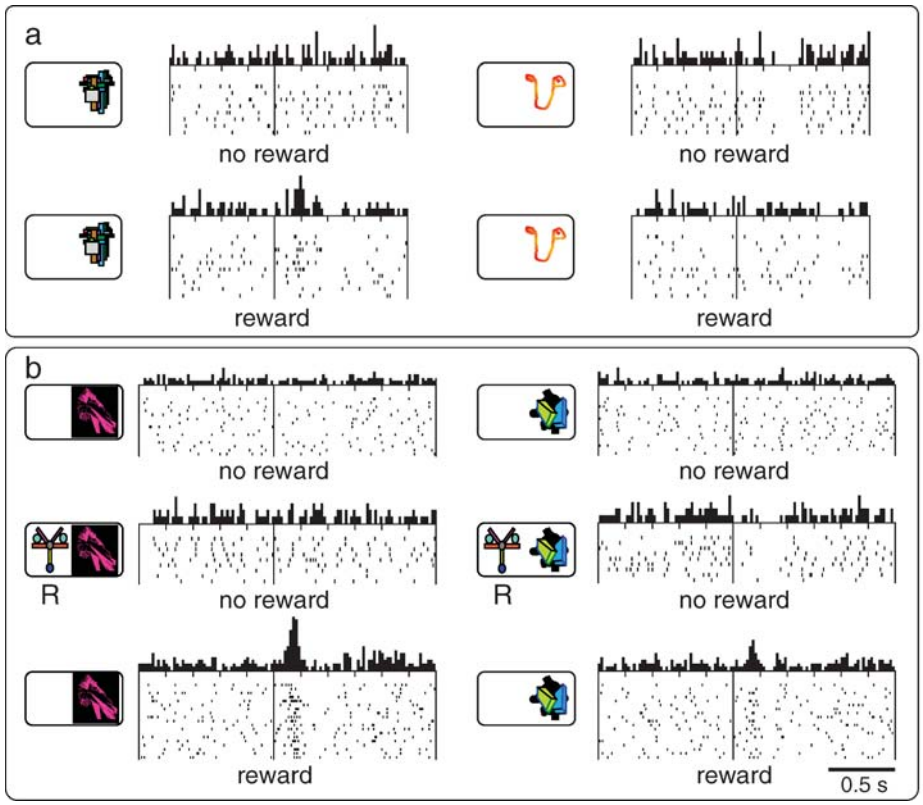

Figure 8 Coding of prediction errors by dopamine neurons in specific paradigms. (a) Blocking test. Lack of response to absence of reward following the blocked stimulus, but positive signal to delivery of reward (left), in contrast to control trials with a learned stimulus (right). Data from Waelti et al. 2001. (b) Conditioned inhibition task. Lack of response to absence of reward following the stimulus predicting no reward (top), even if the stimulus is paired with an otherwise reward-predicting stimulus (R, middle, summation test), but strong activation to reward following a stimulus predicting no reward (bottom). These responses contrast with those following the neutral control stimulus (right). Data from Tobler et al. (2003).

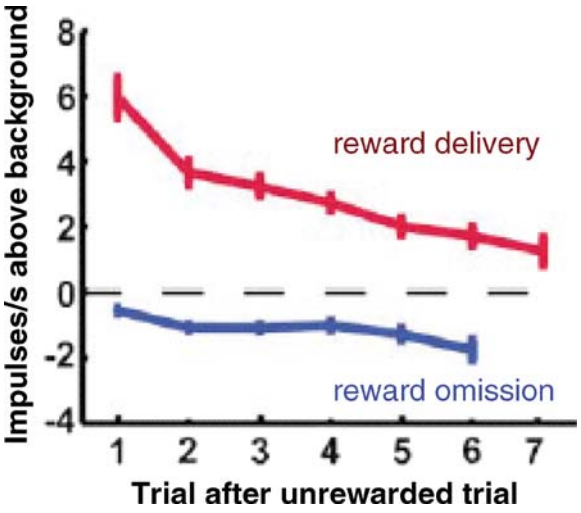

Figure 9 Time information contained in predictions acting on dopamine neurons. In the particular behavioral task, the probability of reward, and thus the reward prediction, increases with increasing numbers of trials after the last reward, reaching p = 1.0 after six unrewarded trials. Accordingly, the positive dopamine error response to a rewarding event decreases over consecutive trials (upper curve), and the negative response to a nonrewarding event becomes more prominent (lower curve). Data are averaged from 32 dopamine neurons studied by Nakahara et al. (2004), □ Cell. Press.

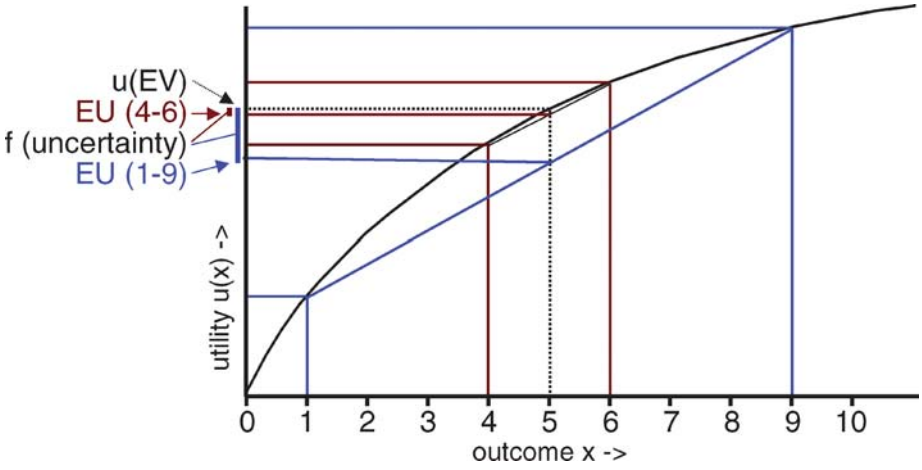

Figure 12 A hypothetical concave utility function. EV, expected value (5 in both gambles with outcomes of 1 and 9, and 4 and 6); EU, expected utility. See text for description.

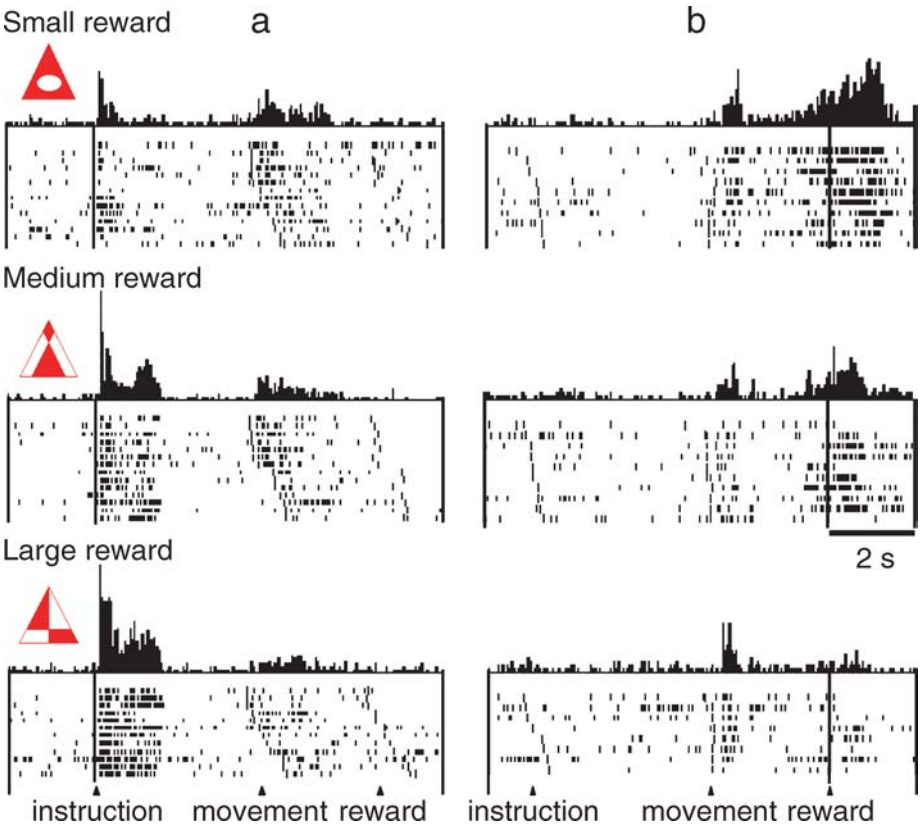

Figure 13 Discrimination of reward magnitude by striatal neurons. (a) Increasing response in a caudate neuron to instruction cues predicting increasing magnitudes of reward (0.12, 0.18, 0.24 ml). (b) Decreasing response in a ventral striatum neuron to rewards with increasing volumes. Data from Cromwell & Schultz 2003.

REVIEW

Milestones in Research on the Pathophysiology of Parkinson's Disease

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ABSTRACT: Progress in our understanding of the mechanisms underlying the cardinal motor abnormalities of Parkinson's disease (PD), in particular akinesia and bradykinesia and their treatment, has been remarkable. Notable accomplishments include insights into the functional organization of the basal ganglia and their place in the motor system as components of a family of parallel cortico-subcortical circuits that subserve motor and nonmotor functions and the development of models of the intrinsic organization of the basal ganglia, including delineation of the so-called direct, indirect, and hyperdirect pathways. Studies in primate models of PD have provided insight into the alterations of neuronal activity that are responsible for the motor features of PD, revealing both altered tonic levels of discharge and significant disturbances of the patterns of discharge throughout the motor circuitry and have led to the formulation of circuit models of PD, providing testable hypotheses for research and stimulating the development of new therapies. Most importantly, the discovery that lesions of the subthalamic nucleus, a key node of the indirect pathway, abolish the cardinal features of PD contributed to the renaissance in the use of surgical approaches to treating patients with PD, including ablation and deep brain stimulation.

Key Words: basal ganglia; direct pathway; indirect pathway; dyskinesias; deep brain stimulation; pallidotomy

Over the past decades, there has been considerable progress in our understanding of the pathophysiology of Parkinson's disease (PD). The refinement of pathophysiologic circuit models has provided testable hypotheses for research and stimulated the search for new therapies. In this article, we will highlight major milestones of discovery in this process.

The term *pathophysiology* will be used in a restricted sense, to refer to the anatomic localization and physiologic changes in neuronal activity in the basal ganglia and related structures that occur in response to the dopamine loss seen in PD. Dopamine loss is thought to result in the motor aspects of the disorder, in particular, the cardinal features of bradykinesia and akinesia. Although PD encompasses a spectrum of other motor and nonmotor manifestations that are largely nondopaminergic in origin,[1–6] our understanding of the pathophysiologic origin of these alterations remains very limited and will not be discussed.

Models of Basal Ganglia Circuitry

The development of a better understanding of the functional organization of the basal ganglia was highly important in the quest for testable pathophysiological models. In this section we briefly review these important insights into the anatomy and function of the basal ganglia and associated areas in the thalamus and cortex. In subsequent sections, the pathophysiologic significance of this knowledge will be elaborated. A major step in this direction was the insight that the

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Relevant conflicts of interest/financial disclosures: Nothing to report. Writing this article was supported in part by NIH/NINDS grants R01NS054976 and P50NS071669 (to T.W.) and an infrastructure grant to the Yerkes National Primate Research Center (NIH/NCRR grant RR-000165). Full financial disclosures and author roles may be found in the online version of this article.

Received: 25 January 2011; **Accepted:** 6 February 2011
Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/mds.23695

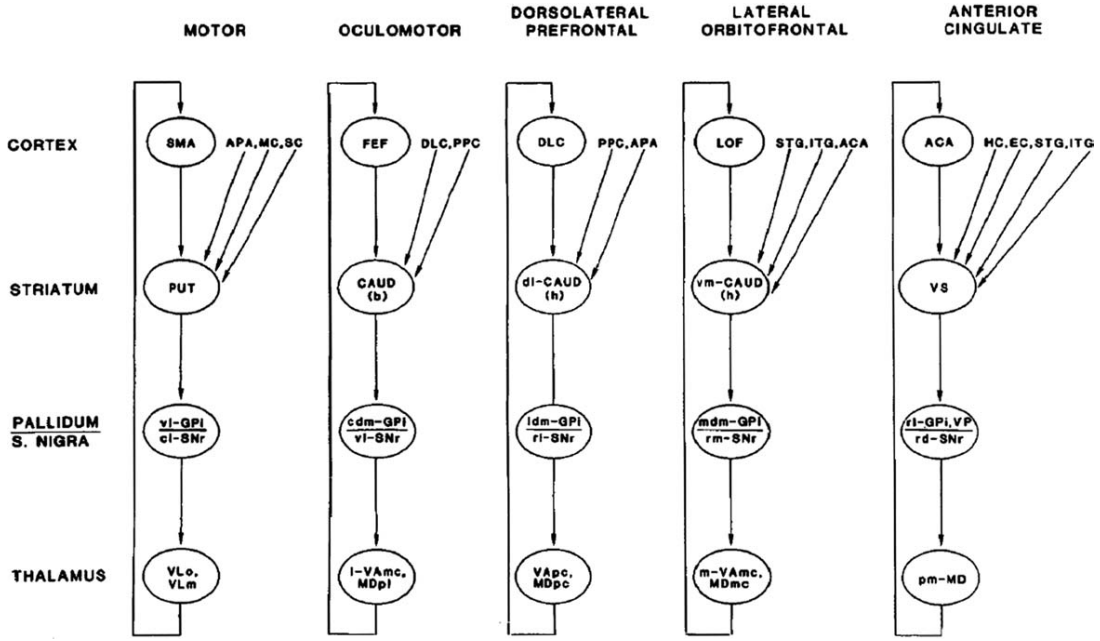

FIG. 1. Basal ganglia–thalamocortical circuits as proposed by Alexander et al in 1986.[8] See text for details. Abbreviations: ACA, anterior cingulate area; APA, arcuate premotor area; CAUD, caudate nucleus (b) body (h) head; DLC, dorsolateral prefrontal cortex; EC, entorhinal cortex; FEF, frontal eye fields; GPi, internal segment of globus pallidus; HC, hippocampal cortex; ITG, inferior temporal gyrus; LOF, lateral orbitofrontal cortex; MC; motor cortex; MDpl, medialis dorsalis pars paralamellaris; MDmc, medialis dorsalis pars magnocellularis; MDpc, medialis dorsalis pars parvocellularisl PPC, posterior parietal cortex; PUT, putamen; SC, somatosensory cortex; SMA, supplementary motor area; SNr, substantia nigra pars reticulata; STG, superior temporal gyrus; VAmc, ventralis anterior pars magnocellularis; VApc, ventralis anterior pars parvocellularis; VLm, ventralis lateralis pars medialis; VLo, ventralis lateralis pars oralis; VP, ventral pallidum; VS, ventral striatum; cl-, caudolateral; cdm-, cudal dorsomedial; dl-, dorsolateral; l-, lateral; ldm-, lateral dorsomedial; m-, medial; mdm-, medial dorsomedial; pm, posteromedial; rd-, rostrodorsal; rl-, rostrolateral; rm-, rostromedial; vm-, ventromedial; vl-, ventrolateral. The figure and legend were originally published in Alexander et al[8] and are used here with permission.

portions of the basal ganglia that are involved in movement are separate from the nonmotor areas and that basal ganglia circuits are (largely) separate from those of the cerebellum. Building on electrophysiologic studies in the primate, which revealed a somatotopic organization of basal ganglia neurons related to movement of individual body parts and highly specific relations to aspects of movement,[7] and on a review of the available anatomic data, a model was proposed in the mid-1980s in which the basal ganglia are viewed as components of segregated circuits that subserve different functions, determined by the functional role of the respective cortical area of origin of the different circuits.[8] This ''parallel-circuit'' hypothesis (Fig. 1) identified discrete cortico-basal ganglia–thalamocortical circuits, subserving skeletomotor, oculomotor, associative (executive), and limbic functions. Although at the time it was believed that the motor circuit targeted only the supplementary motor area (as shown in Fig. 1, a reproduction of a figure from the original article), it is now clear that the motor circuit is, in fact, comprised of subcircuits centered on different precentral motor fields.[9–13] It is accepted that the parallel-circuit hypothesis offers an anatomical explanation for the common development of behavioral, cognitive, and limbic features in basal ganglia disorders and for the prominence of motor features in the clinical presentation of PD because the earliest and most extensive loss of dopamine in the striatum occurs in the postcommissural putamen,[14,15] the striatal portion of the motor circuit.

In addition to the overall circuit organization, the intrinsic connections of the basal ganglia were elucidated in the 1980s and early 1990s, with the formulation of the model of ''direct'' and ''indirect'' striatal output pathways,[16–18] by which the striatum, the principal basal ganglia input structure, is linked to the basal ganglia output structures, that is, the internal pallidal segment (GPi) and the substantia nigra pars reticulata (SNr). The direct and indirect pathways were shown to originate from separate populations of striatal medium spiny neurons (MSNs) whose activity is differentially modulated by dopamine.[19] The direct pathway is a monosynaptic inhibitory projection between MSNs that contain substance-P and dopamine D1-receptors, and GPi/SNr neurons. The indirect pathway is a polysynaptic connection that involves an inhibitory projection from MSNs that express dopamine D2-receptors and enkephalin to the neurons in the external pallidal segment (GPe), and subsequent inhibitory projections between GPe and GPi/SNr, either directly or via the intercalated glutamatergic subthalamic nucleus (STN; Fig. 2A, reproduced from the original figure in Bergman et al[20]).

The anatomical presence of direct and indirect pathways has been hypothesized to have substantial

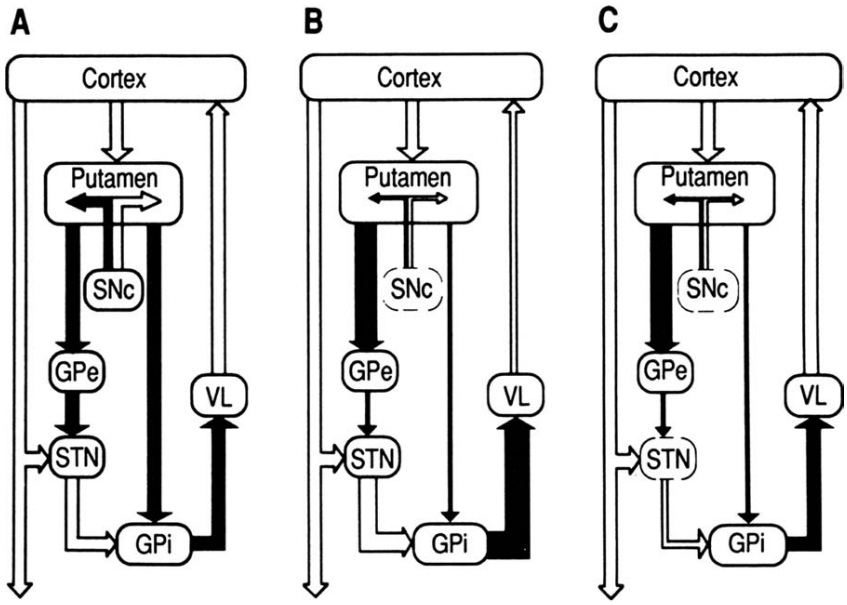

FIG. 2. Functional connectivity within the basal ganglia—thalamocortical circuits under normal and parkinsonian conditions, as proposed by Bergman et al (1990).[20] **A:** Normal (open arrows, excitatory collections; filled arrows, inhibitory collections. SNc, substantia nigra pars compacta; VL, ventrolateral nucleus of the thalamus). The putamen (the "input" stage of the circuit) is connected with GPi (the "output" stage) by direct and indirect projections (via GPe and the STN). The postulated differential effects of dopamine on the 2 striatal systems are indicated schematically. **B:** MPTP-induced parkinsonism. After treatment with MPTP, the SNc was damaged. Resulting changes in the overall activity in individual projection systems are indicated as changes in the width of arrows. Inactivation of the nigroputamenal projection increased GPi activity, secondary to an increase in excitatory drive from the STN and a decrease in direct inhibitory input from the striatum. The resulting overinhibition of thalamocortical circuits may account for some of the parkinsonian motor signs. **C:** Effect of STN lesions in parkinsonism. Inactivation of the STN reduced GPi output to the thalamus toward more normal levels, thus reducing parkinsonian motor signs. The figure and legend were originally published in Bergman et al[20] and are used here with permission.

functional consequences. Activation of MSNs that give rise to the direct pathway would result in the inhibition of GPi and SNr neurons that, in turn, may lead to reduced inhibition of thalamocortical projection neurons and thus to facilitation of movement. Because of the polarities of the connections involved, activation of the indirect pathway would have the opposite effect, that is, an increase of basal ganglia output and suppression of movement.[16–18]

Another anatomical pathway that may have a substantial role in the control of basal ganglia output is the so-called hyperdirect pathway, which includes a cortico-subthalamic connection.[21–23] Activation of this pathway would also act to increase basal ganglia output, resulting in greater inhibition of thalamocortical activities. Although these actions are similar in polarity to those of the indirect pathway, they are considered to be much faster than those mediated by the indirect pathway because they circumvent the relatively slow processing in the striatum and GPe.

With the introduction of transgenic animals in which the direct and indirect pathways can be visualized in brain slice recording studies, a large number of functional differences between the MSNs that give rise to these pathways have been found,[24–29] which may explain their respective involvement in the normal functions of the basal ganglia and in some aspects of the pathophysiology of parkinsonism. In vivo evidence for such differences is largely lacking at this time but should be forthcoming with the help of novel optogenetic and other techniques (see, eg, Kravitz et al[30]).

The Rate Model of Parkinsonism

In the 1960s it had been established that the striatal dopamine content was decreased in patients with PD and that the cardinal features of the disorder could be reversed with administration of levodopa, a precursor of dopamine.[15,31–33] The subsequent development of pathophysiologic models of PD benefited greatly from animal models of dopamine depletion. Among these, the model created by treating primates with the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has had the greatest impact.[34–36]

An important insight gained from studies in such animals was the demonstration of changes in the uptake of 2-deoxyglucose (2DG) in individual basal ganglia nuclei, which mainly reflects the amount of afferent activities in a given area. Studies by Alan Crossman and colleagues showed that 2DG uptake was increased in the GPe, GPi, and ventral anterior and ventral lateral thalamic nuclei[37–40] and was reduced in the STN.[39,40] Subsequent electrophysiological recordings of neuronal activity in MPTP-treated primates confirmed that the spontaneous neuronal

activity in the STN and GPi are increased, whereas that in the GPe is decreased.[41–43] Together, these metabolic and electrophysiologic data suggested that the MSNs that give rise to the indirect pathway are overactive, leading to inhibition of GPe neurons, which, in turn, results in disinhibition of the STN and excessive excitation of the GPi. The resulting increased basal ganglia output to the thalamus was thought to then excessively inhibit thalamic neurons projecting to the cerebral cortex.

In contrast to this model of PD, in which *increased* basal ganglia output led to a reduction of movement, studies of changes in metabolism or electrophysiologic activity found *reduced* basal ganglia output in animal models of hyperkinetic states, such as experimentally induced chorea, hemiballism, and levodopa-induced dyskinesias in monkeys.[44–49] Both lines of evidence led to the development of new concepts about the pathophysiology of PD, strongly linked to the proposed organization of these structures into direct and indirect pathways. These pathophysiologic models were summarized in two landmark review articles, by Albin, Penney, and Young[17] in 1989 and by DeLong in 1990,[18] which described the global activity changes of basal ganglia nuclei in movement disorders. In these articles and subsequent reviews on this topic (eg, Obeso et al[50]), striatal dopamine depletion was postulated to result in increased inhibitory activity over the indirect pathway and decreased activity over the direct pathway, leading to increased inhibitory output from the GPi to the thalamus. In contrast, hyperkinetic disorders such as hemiballismus, chorea, and drug-induced dyskinesias were postulated to result from decreased GPi output (Fig. 2B). The development of these models greatly stimulated further investigations into the pathophysiology of PD.

The proposed role of increased activity in the STN and GPi in parkinsonism was strongly supported by positron emission tomography (PET) studies[51] and by experiments showing that lesions of the STN in MPTP-treated primates almost instantaneously and substantially ameliorate the cardinal motor signs of parkinsonism[20,52–54] (Fig. 2C) and reduce activity in the basal ganglia output nuclei toward more normal levels.[52,54] These lesion studies helped to rekindle the interest of neurosurgeons and neurologists in lesioning approaches for patients with advanced PD, which had largely lain dormant since the introduction of levodopa treatment for PD.[55–60] This first resulted in the reintroduction of GPi pallidotomy, which had clinical effects similar to STN lesions in primates. Lesioning of the STN has also been used as a treatment in patients with PD. Interestingly, such lesions are well tolerated and are not, as initially feared, associated with severe hemiballism in most cases.[60]

Soon after the reintroduction of ablative treatments for PD, the first trials of chronic high-frequency electrical stimulation (deep brain stimulation [DBS]) of basal ganglia targets were carried out in parkinsonian patients. DBS had been employed earlier for movement disorders in the thalamus for treatment of tremor.[61,62] Based on the notion that chronic high-frequency stimulation may have inhibitory effects on the stimulated brain area and a study demonstrating therapeutic effects of high-frequency stimulation of the STN in MPTP-treated monkeys,[63] a group led by Benabid and Pollak carried out a trial of STN-DBS in PD patients.[64] This study and a large body of literature published since then demonstrated substantial and sustained benefits of DBS that are very similar to those obtained by lesioning the STN.[58–60] Because DBS has the advantage of being reversible and adjustable, this technique has now largely replaced ablative surgery for patients with advanced PD in many parts of the world.[65–67]

Pattern Abnormalities and Neuronal Synchrony

Soon after the formulation of the rate model, the researchers started to identify significant inconsistencies with this model, in particular, that lesions of the motor thalamus do not result in akinesia and that lesions of the GPi do not result in dyskinesias.[50,68–70] This realization shifted the attention of researchers to disturbances of neuronal activity in the basal ganglia other than changes in the spontaneous frequency of discharge. In fact, even the earliest studies of basal ganglia dysfunction in MPTP-treated animals had shown that basal ganglia neurons in the parkinsonian state exhibit prominent alterations of their discharge patterns.[41,43,71] Some of these changes are exemplified in the single-cell recordings from parkinsonian primates in Figure 3. One of the principal changes is a greater tendency of neurons in the GPe, STN, GPi, SNr, and basal ganglia-receiving areas of the thalamus to discharge in bursts.[72] The physiological mechanisms underlying this phenomenon are not clear, but rebound burst generation, that is, the transient production of excessive spiking activity following a period of strong inhibition, is likely to play a significant role and has been demonstrated to occur in GPe, GPi, STN, and thalamic neurons.[73–77]

Another prominent change in neuronal activity is that the discharge of basal ganglia neurons becomes more synchronous in the parkinsonian state. Under normal conditions, most neurons in these nuclei discharge independently, but in parkinsonian animals and in human patients with PD, neuronal synchrony is frequently observed in both the basal ganglia and the cortex.[71,78–84] In a sense, dopamine appears to act to maintain the segregation of neuronal activities, which then breaks down in its absence.

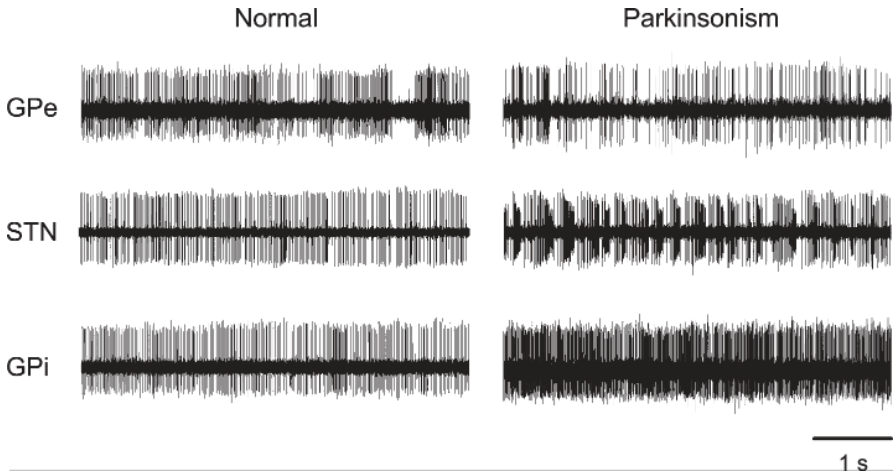

FIG. 3. Changes in the activity of single cells in GPe, STN, or GPi of MPTP-treated monkeys. Shown are example recordings of separate neurons, recorded with standard methods for extracellular electrophysiologic recording in normal and parkinsonian animals. Each data segment is 5 seconds in duration. This figure and the legend were originally published in Galvan and Wichmann[115] and are used here with permission.

In addition, neurons in the basal ganglia, thalamus, and cortex also develop abnormal oscillatory firing patterns, particularly in the alpha- and beta-range of frequencies (eg, Bergman et al,[71] Gatev et al,[85] and Rivlin-Etzion et al[86]). The idea that oscillatory bursts and the synchrony of basal ganglia activities may be important in the pathophysiology of parkinsonism was further developed in the early 2000s, when Brown and colleagues reported that local field potentials (LFPs), recorded from implanted DBS macro-electrodes in the STN of PD patients, indicated synchronized oscillatory activities of large populations of neural elements in and around this structure.[87] Abnormal beta-frequency oscillations can be detected in recordings from unmedicated parkinsonian patients. The oscillations are reduced by levodopa treatment, whereas gamma-band oscillations are increased[87] (Fig. 4). Subsequent studies have documented that similar oscillations also occur in the GPi and cortex of PD patients. Together with the previous single-cell recordings studies, these findings suggested that the basal ganglia–thalamocortical circuitry may be engaged in hypersynchronized pathological oscillations that disturb normal movement-related activities in PD.[88,89] Since the original description by Brown and colleagues, other studies have shown that abnormal oscillatory activity and synchronization of the basal ganglia do not only characterize the parkinsonian state but are also found (at different frequencies) in association with levodopa-induced dyskinesias (Fig. 4)[90] and impulse control disorders in PD.[91] It needs to be mentioned, however, that although hypersynchronized oscillatory activities occur in PD, it is not (yet) established that they are necessary and sufficient to produce parkinsonism. Thus, studies in MPTP-treated monkeys have suggested that such activities may occur relatively late in the process of developing parkinsonism (or may not develop at all, despite the presence of parkinsonian signs, according to unpublished data and Leblois et al[92]). Acute dopamine depletion in rats has also been shown to result in disturbances of motor function without the development of abnormal oscillatory activities.[93]

It is worth noting that in both the "rate" model and in the newer models based on firing pattern abnormalities, activity changes in the indirect pathway are specifically implicated in the development of the major motor features of PD. The importance of indirect pathway dysfunction is further supported by the finding that STN lesions or DBS successfully ameliorates parkinsonian motor features. Recent studies in mice using optogenetic techniques have also demonstrated that activation of indirect-pathway MSNs results in bradykinesia and reduced locomotion in otherwise normal animals, whereas activation of direct-pathway neurons reduces freezing and increases locomotion in animal models of PD.[30]

Akinesia as a Disorder of "Focusing"

The idea that activation of the direct pathway is mainly responsible for movement *facilitation* whereas activation of the indirect pathway *suppresses* movement and that disturbances of the balance between these functions contribute to the pathophysiology of PD and other movement disorders is an essential part of the aforementioned rate model, and, as described above, became established as a fundamental scheme of the physiologic functions of the basal ganglia.[18,94,95] The functional implications of the direct/indirect pathway model were further elaborated by Mink and Thach, who proposed that the basal ganglia may act to "focus" movements through the interplay of the facilitatory actions of the direct pathway and the

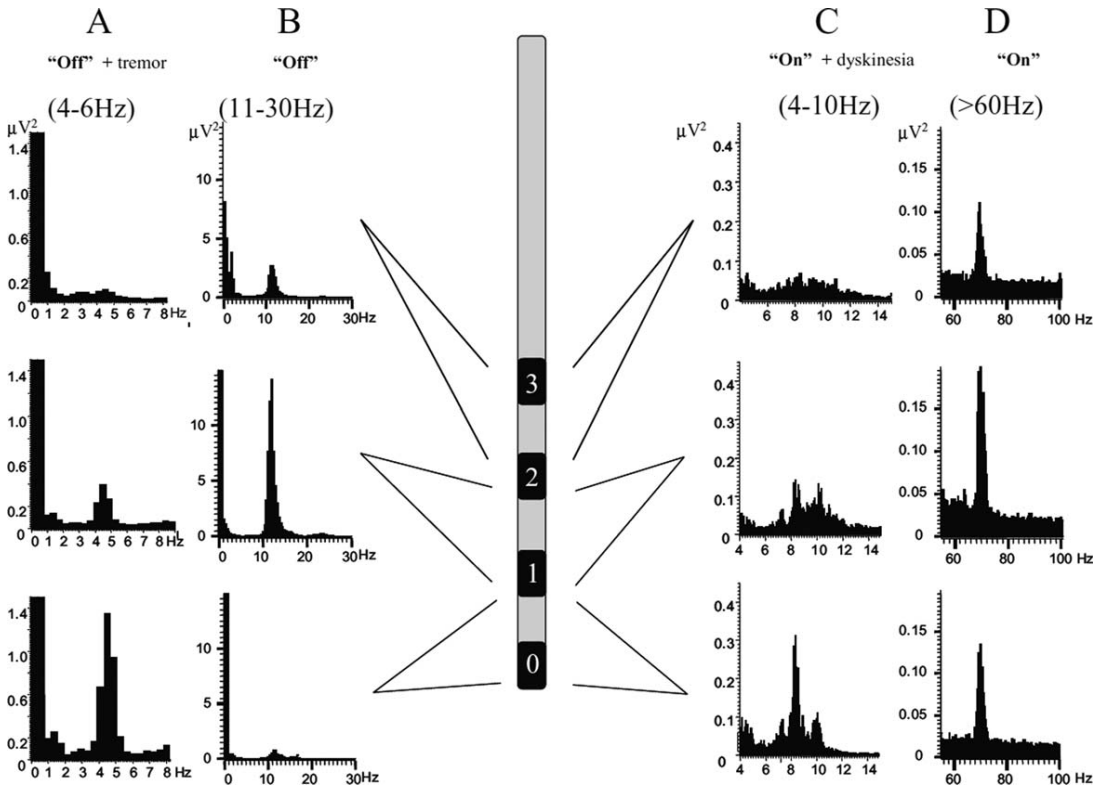

FIG. 4. Oscillatory local field potential activity in the subthalamic nucleus. Shown is the evolution of the LFP autospectra throughout the "off–on" cycle and the predominant site of recording with respect to 3 bipolar contacts in the STN. In the "off" motor state (left) in a patient with tremor (**A**), there is a predominant peak at around 5 Hz, whereas in a patient without tremor (**B**), there is only a peak at around 11–12 Hz that is maximal at the second-most dorsal STN contact. In the "on" + dyskinesias motor state (right), the same patient shown in **B** exhibited a 4- to 10-Hz peak predominantly at the ventral recording site (**C**) and a 60- to 80-Hz peak at all 3 sites, although the middle contact predominated (**D**). This figure and the legend were originally published in Alonso-Frech et al[90] and are used here with permission.

suppressive actions of the indirect and hyperdirect pathways.[22,96,97] This model is also championed by studies by Nambu et al., based on studies of the effects of electrical motor cortex stimulation on basal ganglia activities in monkeys.[22,97,98] Akinesia could then be understood as a dopamine-depletion-induced imbalance of the two main striatopallidal systems, in which overly restrictive focusing via the indirect pathway leads to suppression of intended movements.[99] Although this focusing model of basal ganglia function and dysfunction has gained considerable attention, it remains controversial. The fact that GPi lesions in primates and posteroventral pallidotomy in PD patients are not associated with obvious deleterious effects on movement or posture, and the well-documented late onset of GPi discharge in relation to movement onset, are major inconsistencies of this hypothesis.

Parkinsonism Interpreted as Disorder of Basal Ganglia Interference with Cortical Functions

Soon after the initial publication of the rate model, Marsden and Obeso discussed that the model was at odds with the finding that lesions of the motor thalamus do not cause or worsen akinesia.[70] These observations suggested that the basal ganglia may not directly facilitate or inhibit movement, but may aid cortical operations more subtly in the acquisition and execution of automatic movements and the adjustment of behavior to the occurrence of unexpected events. The abnormal activity of the basal ganglia in PD may simply interfere with cortical operations. Surgical disruption of the basal ganglia–thalamocortical connections by lesioning or DBS would free cortical operations from subcortical "noise." Of course, surgical elimination of basal ganglia output would also be expected to eliminate the contribution of the basal ganglia–thalamocortical system to normal behavior, potentially resulting in deficits in motor learning and an inability of directing actions to novel events. In fact, recent studies have documented that patients with PD preferentially lose functions of the dorsolateral striatum, including specifically the learning and execution of habits and procedures (reviewed in Redgrave et al[100]) and that PD patients with therapeutic near-complete lesions of the basal ganglia motor output through combined pallidotomy/subthalamotomy procedures[101,102] show further reductions in implicit learning.

Other Aspects of PD Pathophysiology

The loss of dopamine not only influences the functional balance between direct, indirect, and hyperdirect pathways and spontaneous firing patterns of the basal ganglia, but also affects the anatomical integrity of striatal (and probably other basal ganglia) cells. Thus, studies in animal models of dopamine loss and in patients with PD have demonstrated a loss of dendritic spines on striatal MSNs.[103–109] In rodent preparations, this anatomical change may particularly affect MSNs that give rise to the indirect pathway,[108] but in MPTP-treated monkeys the process of spine elimination appears to be less specific.[103] Spine loss may have significant consequences on synaptic plasticity and adaptive changes in the striatum and may contribute to the aforementioned learning deficits in PD patients (also see above). In addition to the neuronal degeneration in the substantia nigra pars compacta, cell loss has also been documented to occur in other brain areas, such as the intralaminar nuclei of the thalamus, both in patients with PD and in animal models of dopamine depletion.[110,111] The functional significance of these changes and their apparent link to the dopamine cell loss remain unclear.

In recent years it has also been recognized that dopamine loss outside the striatum may be involved in the pathophysiology of parkinsonism. Rodent and monkey studies have suggested that dopamine has substantial effects on neuronal firing in the GPe, GPi, and SNr, and perhaps also in the STN (reviewed in Rommelfanger et al[112]). The dopamine concentrations at these locations is much smaller than that in the striatum,[113] so that the ultimate effect of the loss of endogenous dopamine in these areas is not clear. However, dopamine receptor activation by dopaminergic therapies in parkinsonism is likely to have strong effects in these areas and may contribute to the antiparkinsonian and adverse effects of these agents.

Conclusions

Our knowledge of changes in brain activity that develop as a consequence of dopamine loss has greatly expanded over the last decades, although we are far from a comprehensive mechanistic understanding of the pathophysiology of PD. However, the development of the models mentioned above has significantly altered our approach to treating parkinsonian patients. Thus, the models have helped with the development of some of the currently used medication treatments and are being used to develop new ones, aimed at amplifying or modulating the responses to dopaminergic treatments (for instance, adenosinergic drugs or metabotropic glutamate receptor agents). Perhaps the most significant impact of these studies and models has been that they helped to revive interest in neurosurgical treatments and guided targeting of surgical approaches to the motor portions of the basal ganglia and thalamus, leading to more effective treatment of tens of thousands of patients with advanced PD.

In the future, other basic issues need to be addressed, including questions about the relevance of the loss of dopamine for cognitive and executive function, mood regulation, and learning (eg, Knowlton et al[114]) and the origin of motor manifestations that are not sensitive to dopaminergic and surgical treatments. It is hoped that the application of novel experimental approaches, such as optogenetic techniques, which are able to dissect with greater specificity the activity and role of specific neuronal components of the larger circuits, will address these and other issues.[30]

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