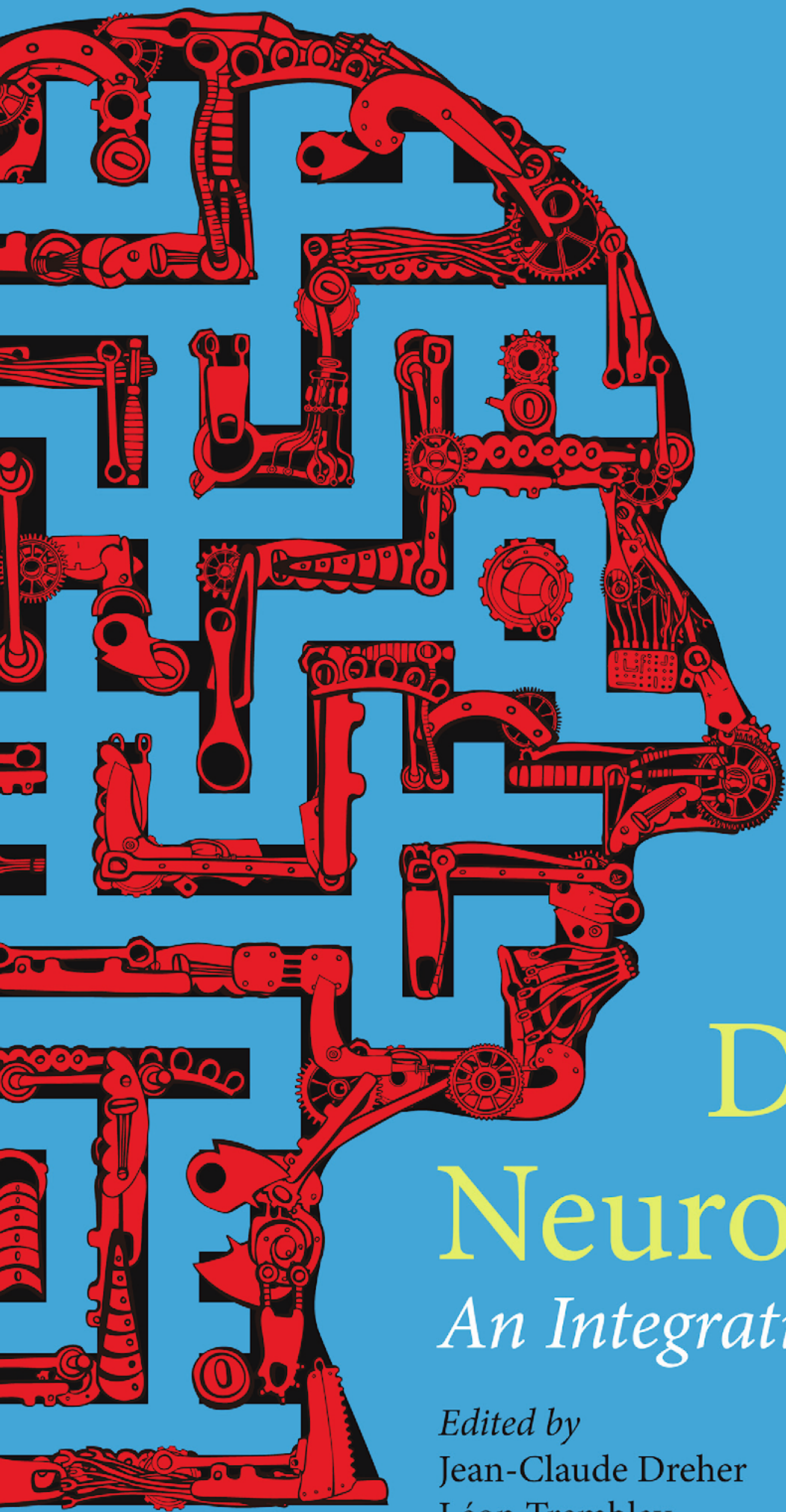

Decision Neuroscience

An Integrative Perspective

Edited by
Jean-Claude Dreher
Léon Tremblay

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DECISION NEUROSCIENCE

AN INTEGRATIVE PERSPECTIVE

Edited by

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Preface

Decision Neuroscience: an Integrative Perspective addresses fundamental questions about how the brain makes perceptual, value-based, and more complex decisions in nonsocial and social contexts. This book presents recent and compelling neuroimaging, electrophysiological, lesional, and neurocomputational studies, in combination with hormonal and genetic studies, that have led to a clearer understanding of the neural mechanisms behind how the brain makes decisions. The neural mechanisms underlying decision-making processes are of critical interest to scientists because of the fundamental role that reward plays in a number of cognitive processes (such as motivation, action selection, and learning) and because they have theoretical and clinical implications for understanding dysfunctions of major neurological and psychiatric disorders.

The idea for this book grew up from our edition of the *Handbook of Reward and Decision Making* (Academic Press, 2009). We originally thought to revise and reedit this book, addressing one fundamental question about the nature of behavior: how does the brain process reward and makes decisions when facing multiple options? However, given the developments in this active area of research, we decided to feature an entirely different book with new contents, covering results on the neural substrates of rewards and punishments; perceptual, value-based, and social decision-making; clinical aspects such as behavioral addictions; and the roles of genes and hormones in these various aspects. For example, an exciting topic from the field of social neuroscience is to know whether the neural structures engaged with various forms of social interactions are cause or consequence of these interactions (Fernald, Chapter 28).

A mechanistic understanding of the neural encoding underlying decision-making processes is of great interest to a broad readership because of their theoretical and clinical implications. Findings in this research field are also important to basic neuroscientists interested in how the brain reaches decisions, cognitive psychologists working on decision-making, as well as computational neuroscientists studying probabilistic models of brain functions. Decision-making covers a wide range of topics and levels of analysis, from molecular mechanisms to neural systems dynamics, neurocomputational models, and social system levels. The contributions to this book are forward-looking assessments of the current and future issues faced by researchers. We were fortunate to assemble an outstanding collection of experts who addressed various aspects of decision-making processes. The book is divided into five parts that address distinct but interrelated topics.

STRUCTURE OF THE BOOK

A decision neuroscience perspective requires multiple levels of analyses spanning neuroimaging, electrophysiological, behavioral, and pharmacological techniques, in combination with molecular and genetic tools. These approaches have begun to build a mechanistic understanding of individual and social decision-making. This book highlights some of these advancements that have led to the current understanding of the neuronal mechanisms underlying motivational and decision-making processes.

Part I is devoted to animal studies (anatomical, neurophysiological, pharmacological, and optogenetics) on rewards/punishments and decision-making. In their natural environment, animals face a multitude of stimuli, very few of which are likely to be useful as predictors of reward or punishment. It is thus crucial that the brain learns to predict rewards, providing a critical evolutionary advantage for survival. This first part of the book offers a comprehensive view of the specific contributions of various brain structures as the dopaminergic midbrain neurons, the amygdala, the ventral striatum, and the prefrontal cortex, including the lateral prefrontal cortex and the orbitofrontal cortex, to the component processes underlying reinforcement-guided decision-making, such as the representation of instructions, expectations, and outcomes; the updating of action values; and the evaluation process guiding choices between prospective rewards. Special emphasis is made on the neuroanatomy of the reward system and the fundamental roles of dopaminergic neurons and the basal ganglia in learning stimulus–reward associations.

Chapter 1 (Haber SN) describes the anatomy and connectivity of the reward circuit in nonhuman primates. It describes how cortical–basal ganglia loops are

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topographically organized and the key areas of convergence between functional regions.

Chapter 2 describes three novel electrophysiological properties of the classical dopamine reward-prediction error (RPE) signal (Schultz W). Studies have identified three novel properties of the dopamine RPE signal. In particular, concerning its roles in making choices, the dopamine RPE signal may not only reflect subjective reward value and formal economic utility but could also fit into formal competitive decision models. The RPE signal may code the chosen value suitable for updating or immediately influencing object and action values. Thus, the dopamine utility prediction error signal bridges the gap between animal learning theory and economic decision theory.

Chapter 3 focuses on the electrophysiological properties of another important component of the reward system in primates, namely the amygdala (Bernardi S and Salzman D). The amygdala contains distinct appetitive and aversive networks of neurons. Processing in these two amygdalar networks can both regulate and be regulated by diverse cognitive operations.

Chapter 4 extends the concept of appetitive and aversive motivational processes to the striatum (Saga Y and Tremblay L). This chapter describes how the ventral striatum and the ventral pallidum, two parts of the limbic circuit in the basal ganglia, are involved not only in appetitive rewarding behavior, as classically believed, but also in negative motivational behavior. These results can be linked with the control of approach/avoidance behavior in a normal context and with the expression of anxiety-related disorders. The disturbance of this pathway may induce not only psychiatric symptoms, but also abnormal value-based decision-making.

Chapter 5 (Tian J, Uchida N, and Eshel N) highlights new advances in the physiology, function, and circuit mechanism of decision-making, focusing especially on the involvement of dopamine and striatal neurons. Using optogenetics in rodents, molecular techniques, and genetic techniques, this chapter shows how these tools have been used to dissect the circuits underlying decision-making. It describes exciting new avenues to understand a circuit, by recording from neurons with knowledge of their cell type and patterns of connectivity. Furthermore, the ability to manipulate the activity of specific neural types provides an important means to test hypotheses of circuit function.

Chapter 6 (Bradfield L and Balleine B) describes the neural bases of the learning and motivational processes controlling goal-directed action. By definition, the performance of such action respects both the current value of its outcome and the extant contingency between that action and its outcome. This chapter identifies the neural circuits mediating distinct processes, including the acquisition of action-outcome contingencies, the encoding and retrieval or incentive value, the matching of that value to specific outcome representations, and finally the integration of this information for action selection. It also shows how each of these individual processes are integrated within the striatum for successful goal-directed action selection.

Chapter 7 (Robbins TW and Dalley JW) describes animal models (mostly in rodents) of impulsivity and risky choices. It reviews the neural and neurochemical basis of various forms of impulsive behavior by distinguishing three main forms of impulsivity: waiting impulsivity, risky choice impulsivity, and stopping impulsivity. It shows that dopamine- and serotonin-dependent functions of the nucleus accumbens are implicated in waiting impulsivity and risky choice impulsivity, as well as cortical structures projecting to the nucleus accumbens. For stopping impulsivity, dopamine-dependent functions of the dorsal striatum are implicated, as well as circuitry including the orbitofrontal cortex and dorsal prelimbic cortex. Differences and commonalities between the forms of impulsive responding are highlighted. Importantly, various applications to human neuropsychiatric disorders such as drug addiction and attention deficit hyperactivity disorder are also discussed.

Chapter 8 (Fuster JM) proposes that the neural mechanisms of decision-making are understandable only in the structural and dynamic context of the perception—action cycle, defined as the biocybernetic processing of information that adapts the organism to its environment. It presents a general view of the role of the prefrontal cortex in decision-making, in the general framework of the perception—action cycle, including prediction, preparation toward decision, execution, and feedback from decision.

Part II covers the topic of the neural representation of motivation, perceptual decision-making, and value-based decision-making in humans, mostly combining neurocomputational models and brain imaging studies.

Chapter 9 (Tobler P and Kahnt T) reviews several definitions of value and salience, and describes human neuroimaging studies that dissociate these variables. Value increases with the magnitude and probability of reward but decreases with the magnitude and probability of punishment, whereas salience increases with the magnitude and probability of both reward and punishment. At the neural level, value signals arise in striatum, orbitofrontal and ventromedial prefrontal cortex, and superior parietal areas, whereas magnitude-based salience signals arise in the anterior cingulate cortex and the inferior parietal cortex. By contrast, probability-based salience signals have been found in the ventromedial prefrontal cortex.

Chapter 10 (Louie K and Glimcher PW) reviews an approach centered on basic computations underlying

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neural value coding. It proposes that neural information processing in valuation and choice relies on computational principles such as contextual modulation and divisive normalization. Divisive normalization is a nonlinear gain control algorithm widely observed in multiple sensory modalities and brain regions. Identification of these computations sheds light on how the underlying neural circuits are organized, and neural activity dynamics provides a link between biological mechanism and computations.

Chapter 11 (Philiastides M, Diaz J, and Gherman S) introduces the general principles guiding perceptual decision-making. Perceptual decisions occur when perceptual inputs are integrated and converted to form a categorical choice. It reviews the influence of a number of factors that interact and contribute to the decision process, such as prestimulus state, reward and punishment, speed–accuracy trade-off, learning and training, confidence, and neuromodulation. It shows how these decision modulators can exert their influence at various stages of processing, in line with predictions derived from sequential-sampling models of decision-making.

Chapter 12 (Summerfield C) reviews the neural and computational mechanisms of perceptual decisions. It addresses current controversial questions, such as how we decide when to draw our decisions to a conclusion, and how perceptual decisions are biased by prior information.

Chapter 13 (Soltani A, Chaisangmongkon W, and Wang XJ) presents possible biophysical and circuit mechanisms of valuation and reward-dependent plasticity underlying adaptive choice behavior. It reviews mathematical models of reward-dependent adaptive choice behavior, and proposes a biologically plausible, reward-modulated Hebbian synaptic plasticity rule. It shows that a decision-making neural circuit endowed with this learning rule is capable of accounting for behavioral and neurophysiological observations in a variety of decision-making tasks.

Part III of the book focuses on the rapidly developing field of social neuroscience, integrating neuroscience data from both nonhuman primates and humans. Primates are fundamentally social animals, and they may share common neural mechanisms in diverse forms of social behavior. Examples of such behavior include tracking intentions and beliefs from others, being observed by others during prosocial decisions, or learning the social hierarchy in a group of individuals. It is also likely that at the macroscopic level, important differences exist concerning social brain structures and connectivity, and there is a need to directly compare between species to answer this fundamental question. Indeed, studies in both humans and monkeys report not only an increase in gray matter density of specific brain structures relative to the size of our social network, but also species differences in prefrontal–temporal brain connectivity. Furthermore, this part of the book presents neurocomputational approaches starting to provide a mechanistic understanding of social decisions. For example, reinforcement learning models and strategic reasoning models can be used when learning social hierarchies or during social interactions.

A social neuroscience understanding requires multiple approaches, such as electrophysiology and neuroimaging in both monkeys (Chapters 14, 15, 19) and humans (Chapters 16, 18, 20), as well as causal (Chapter 21), neurocomputational (Chapters 17–19), endocrinological, genetics, and clinical approaches (Part V).

Chapter 14 (Duhamel JR and colleagues) presents monkey electrophysiological data revealing that the orbitofrontal cortex is tuned to social information. For example, in one experiment, macaque monkeys worked to collect rewards for themselves and two monkey partners. Single neurons encoded the meaning of visual cues that predicted the magnitude of future rewards, the motivational value of rewards obtained in a social context, and the tracking of social preferences and partner's identity and social rank. The orbitofrontal cortex thus contains key neuronal mechanisms for the evaluation of social information. Moreover, macaque monkeys take into account the welfare of their peers when making behavioral choices bringing about pleasant or unpleasant outcomes to a monkey partner. Thus, this chapter reveals that prosocial decision-making is sustained by an intrinsic motivation for social affiliation and controlled through positive and negative vicarious reinforcements.

Chapter 15 (Sallet J and colleagues) reviews the similarities between monkeys and humans in the organization of the social brain. Using MRI-based connectivity methods, they compare human and macaque social areas, such as the organization of the medial prefrontal cortex. They revealed that the connectivity fingerprint of macaque area 10 best matched that of the human frontal pole, suggesting that even high-level areas share features between species. They also showed that animals housed in large social groups had more gray matter volume in bilateral mid-superior temporal sulcus and rostral prefrontal cortex. Beyond species similarities, there are also distinct differences between human and macaque prefrontal–temporal brain connectivity. For example, functional connections between the temporal cortex and the lateral prefrontal cortex are stronger in humans compared to connections with the medial prefrontal cortex in humans, but the opposite pattern is observed in macaques.

Chapter 16 (Izuma K) focuses on two forms of social influence, the audience effect, which is an increased prosocial tendency in front of other people, and social conformity, which consists in adjusting one's attitude or

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behavior to those of a group. This chapter discusses fMRI findings in healthy humans in these two types of social influence and also shows how reputation processing is impaired in individuals with autism. It also links social conformity and reward-based learning (reinforcement learning).

Chapter 17 (Ligneul R and Dreher JC) examines how the brain learns social dominance hierarchies. Social dominance refers to relationships wherein the goals of one individual prevail over the goals of another individual in a systematic manner. Dominance hierarchies have emerged as a major evolutionary force to drive dyadic asymmetries in a social group. This chapter proposes that the emergence of dominance relationships are learned incrementally, by accumulating positive and negative competitive feedbacks associated with specific individuals and other members of the social group. It considers such emergence of social dominance as a reinforcement learning problem inspired by neurocomputational approaches traditionally applied to nonsocial cognition. This chapter also reports how dominance hierarchies induce changes in specific brain systems, and it reviews the literature on interindividual differences in the appraisal of social hierarchies, as well as the underlying modulations of cortisol, testosterone, and serotonin/dopamine systems, which mediate these phenomena.

Chapter 18 (Seo H and Lee D) describes reinforcement learning models and strategic reasoning during social decision-making. It shows that dynamic changes in choices and decision-making strategies can be accounted for by reinforcement learning in a variety of contexts. This framework has also been successfully adopted in a large number of neurobiological studies to characterize the functions of multiple cortical areas and basal ganglia. For complex decision-making, including social interactions, this chapter shows that multiple learning algorithms may operate in parallel.

Chapter 19 (Ugazio G and Ruff C) reports brain stimulation studies on social decision-making, which test the causal relationship between neural activity and different types of processes underlying these decisions, including social emotions, social cognition, and social behavioral control.

Chapter 20 (Chierchia G and Singer T) shows that two important social emotions, empathy and compassion, engage distinct neurobiological mechanisms, as well as different affective and motivational states. Empathy for pain engages a network including the anterior insula and anterior midcingulate cortex, areas associated with negative affect; compassionate states engage the medial orbitofrontal cortex and ventral striatum and are associated with feelings of warmth, concern, and positive affect.

Part IV of the book focuses on clinical aspects involving disorders of decision-making and of the reward system that link together basic research areas, including systems, cognitive, and clinical neuroscience. Dysfunction of the reward system and decision-making is present in a number of neurological and psychiatric disorders, such as Parkinson's disease, schizophrenia, drug addiction, and focal brain lesions. The study of pathological gambling, for example, and other motivated states associated with, and leading to, compulsive behavior provides an opportunity to learn about the dysfunctions of reward system activity, independent of direct pharmacological activation of brain reward circuits. On the other hand, because drugs of abuse directly activate brain systems, they provide a unique challenge in understanding how pharmacological activation influences reward mechanisms leading to persistent compulsive behavior.

Chapter 21 (Murray GK, Tudor-Sfetea C, and Fletcher PC) shows that principles of reinforcement learning are useful to understand the neural mechanisms underlying impaired learning, reward, and motivational processes in schizophrenia. Two symptoms characteristic of this disease is considered in this framework, namely delusions and anhedonia.

Chapter 22 (Vaidya AR and Fellows LK) takes a neuropsychological approach to review focal frontal lobe damage effects on value-based decisions. It reveals the necessary contributions of specific subregions (ventromedial, lateral, and dorsomedial prefrontal cortex) to decision-making, and provides evidence as to the dissociability of component processes. It argues that the ventromedial frontal lobe is required for optimal learning from reward under dynamic conditions and contributes to specific aspects of value-based decision-making. It also shows a necessary contribution of the dorsomedial frontal lobe in representing action-value expectations.

Chapter 23 (Palminteri S and Pessiglione M) reviews reinforcement learning models applied to reward and punishment learning. These studies include fMRI and neural perturbation following drug administration and/or pathological conditions. They propose that distinct brain systems are engaged, one in reward learning (midbrain dopaminergic nuclei and ventral prefrontostriatal circuits) and another in punishment learning, revolving around the anterior insula.

Chapter 24 (Voon V) discusses decision-making impairments and impulse control disorders in Parkinson's disease. The author reports enhancement of the gain associated with levodopa, reinforcing properties of dopaminergic medications, and enhancement of delay discounting in these patients. Lower striatal dopamine transporter levels preceding medication exposure, and decreased midbrain D2 autoreceptor sensitivity, may

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underlie enhanced ventral striatal dopamine release and activity in response to salient reward cues, anticipated and unexpected rewards, and gambling tasks. Impairments in decisional impulsivity (delay discounting, reflection impulsivity, and risk taking) implicate the ventral striatum, orbitofrontal cortex, anterior insula, and dorsal cingulate. These findings provide insight into the role of dopamine in decision-making processes in addiction and suggest potential therapeutic targets.

Chapter 25 (Witt K) reports that motor control is the result of a balance between activation and inhibition of movement patterns. It points to a central role of the subthalamic nucleus within the indirect basal ganglia pathway, acting as a brake on the motor system. This subthalamic nucleus function occurs when an automatic response must be suppressed to have more time to choose between alternative responses.

Chapter 26 (Grupe DW) discusses value-based decision-making as one of a key behavioral symptoms present in anxiety disorders. This chapter highlights alterations to specific processes: decision representation, valuation, action selection, outcome evaluation, and learning. Distinct anxious phenotypes may be characterized by differential alterations to these processes and their associated neurobiological mechanisms.

Chapter 27 (Clark L) presents a conceptualization of disordered gambling as a behavioral addiction driven by an exaggeration of multiple psychological distortions that are characteristic of human decision-making, and underpinned by neural circuitry subserving appetitive behavior, reinforcement learning, and choice selection. The chapter discusses the neurobiological basis of pathological gambling behavior in loss aversion, probability weighting, perceptions of randomness, and the illusion of control.

Part V focuses on the roles of hormones and genes involved in motivation and social decision-making processes. The combination of molecular genetic, endocrinology, and neuroimaging has provided a considerable amount of data that help in the understanding of the biological mechanisms influencing decision processes. These studies have demonstrated that genetic and hormonal variations have an impact on the physiological response of the decision-making system. These variations may account for some of the inter- and intra-individual behavioral differences observed in social cognition.

Chapter 28 (Fernald RD) presents an original approach for cognitive neuroscientists by focusing on the difficult question of how an animal's behavior or perception of its social and physical surroundings shapes its brain. Using a fish model system that depends on complex social interactions, this chapter reports how the social context influences the brain and, in turn, alters the behavior and neural circuitry of animals as they interact. Gathering of social information vicariously produces rapid changes in gene expression in key brain nuclei and these genomic responses prepare the individual to modify its behavior to move into a different social niche. Both social success and failure produce changes in neuronal cell size and connectivity in key brain nuclei. This approach bridges the gap between social information gathering from the environment and the levels of cellular and molecular responses.

Chapter 29 (Rabl U, Ortner N, and Pezawas L) examines the use of imaging genetics to explore the relationships between major depressive disorder and decision-making.

Chapters 30–32 report neuroendocrinological findings in social decision-making, likening variations in the levels of different types of hormones (cortisol, oxytocin, ghrelin/leptin) to brain systems engaged in social decisions and food choices. Chapter 30 (Hermans EJ and colleagues) integrates knowledge of the effects of stress at the neuroendocrine, cellular, brain systems, and behavioral levels to quantify how stress-related neuromodulators trigger time-dependent shifts in the balance between two brain systems: a "salience" network, which supports rapid but rigid decisions, and an "executive control" network, which supports flexible, elaborate decisions. This simple model elucidates paradoxical findings reported in human studies on stress and cognition.

Chapter 31 (Lefevre A and Sirigu A) reviews evidence for a role for oxytocin in individual and social decision-making. It discusses animal and human studies to link the behavioral effects of oxytocin to its underlying neurophysiological mechanisms.

Chapter 32 (Dagher A, Neseliler S, and Han JE) examines the neurobehavioral factors that determine food choices and food intake. It reviews findings on the interactions between brain systems that mediate feeding behavior and the gut and adipose peptides that signal the current state of energy balance.

Chapter 33 (Dreher, Tremblay, and Schultz) concludes this decision neuroscience book by integrating perspectives from all contributors.

We anticipate that while some readers may read the volume from the first to the last chapter, other readers may read only one or more chapters at a time, and not necessarily in the order presented in the book. This is why we encouraged an organization of this volume whereby each chapter can stand alone, while making references to others and minimizing redundancies across the volume. Given the consistent acceleration of advances in the various approaches described in this book on decision neuroscience, you are about to be dazzled by a first look at the new stages of an exciting era in brain research. Enjoy!

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PART I

ANIMAL STUDIES ON REWARDS, PUNISHMENTS, AND DECISION-MAKING

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CHAPTER

1

Anatomy and Connectivity of the Reward Circuit

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Abstract

While cells in many brain regions are responsive to reward, the cortical–basal ganglia circuit is at the heart of the reward system. The key structures in this network are the anterior cingulate cortex, the orbital prefrontal cortex, the ventral striatum, the ventral pallidum, and the midbrain dopamine neurons. In addition, other structures, including the dorsal prefrontal cortex, amygdala, thalamus, and lateral habenular nucleus, are key components in regulating the reward circuit. Connectivity between these areas forms a complex neural network that is topographically organized, thus maintaining functional continuity through the corticobasal ganglia pathway. However, the reward circuit does not work in isolation. The network also contains specific regions in which convergent pathways provide an anatomical substrate for integration across functional domains.

INTRODUCTION

The reward circuit is a complex neural network that underlies the ability to effectively assess the likely outcomes of different choices. A key component to good decision-making and appropriate goal-directed behaviors is the ability to accurately evaluate reward value, predictability, and risk. While the hypothalamus is central for processing information about basic, or primary, rewards higher cortical and subcortical forebrain structures are engaged when complex choices about these fundamental needs are required. Moreover, choices often involve secondary rewards, such as money, power, challenge, etc., that are more abstract (compared to primary needs), and not as dependent on direct sensory stimulation. Although cells that respond to various aspects of reward such as anticipation, value, etc., are found throughout the brain, at the center of this neural network is the ventral corticobasal ganglia circuit. The basal ganglia (BG) are traditionally considered to process information in parallel and segregated functional streams consisting of reward processing, cognition, and motor control areas [1]. Moreover, within the ventral BG, there are microcircuits thought to be associated with various aspects of reward processing. However, a key component for learning and adaptation of goal-directed behaviors is the ability not only to evaluate various aspects of reward but also develop appropriate action plans and inhibit maladaptive choices on the basis of previous experience. This requires integration between various aspects of reward processing as well as interaction between reward circuits and brain regions involved in cognition. Thus, while parallel processing provides throughput channels by which specific actions can be expressed while others are inhibited, the BG also plays a central role in learning new procedures and associations, implying the necessity for integrative processing across circuits. Indeed, we now know that the network contains multiple regions in which integration across circuits occurs [2–8]. Therefore, while the ventral BG network is at the heart of reward processing, it does not work in isolation. This chapter addresses not only the connectivities within this circuit, but also how this circuit anatomically interfaces with other BG circuits. Reward and aversive processes work together in learning and decision-making. Aversive processing associated with punishment and negative outcomes is addressed by other authors in this book.

The frontal–BG network, in general, mediates all aspects of action planning, including reward and motivation, cognition, and motor control. However, specific regions within this network play a unique role in various aspects of reward processing and evaluation of outcomes, including reward value, anticipation, predictability, and risk. The key structures are

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prefrontal areas [anterior cingulate cortex (ACC) and orbital prefrontal cortex (OFC)], the ventral striatum (VS), the ventral pallidum (VP), and the midbrain dopamine (DA) neurons. The ACC and OFC prefrontal areas mediate different aspects of reward-based behaviors, error prediction, value, and the choice between short- and long-term gains. Cells in the VS and VP respond to anticipation of reward and reward detection (see Chapter 4). Reward-prediction and error-detection signals are generated, in part, from the midbrain DA cells (see Schultz in this volume). While the VS and the ventral tegmental area (VTA) DA neurons are the BG areas most commonly associated with reward, reward-responsive activation is not restricted to these, but found throughout the striatum and substantia nigra pars compacta (SNc). In addition, other structures including the dorsal prefrontal cortex (DPFC), amygdala, hippocampus, thalamus, subthalamic nucleus (STN), and lateral habenula (LHb) are part of the reward circuit (Fig. 1.1).

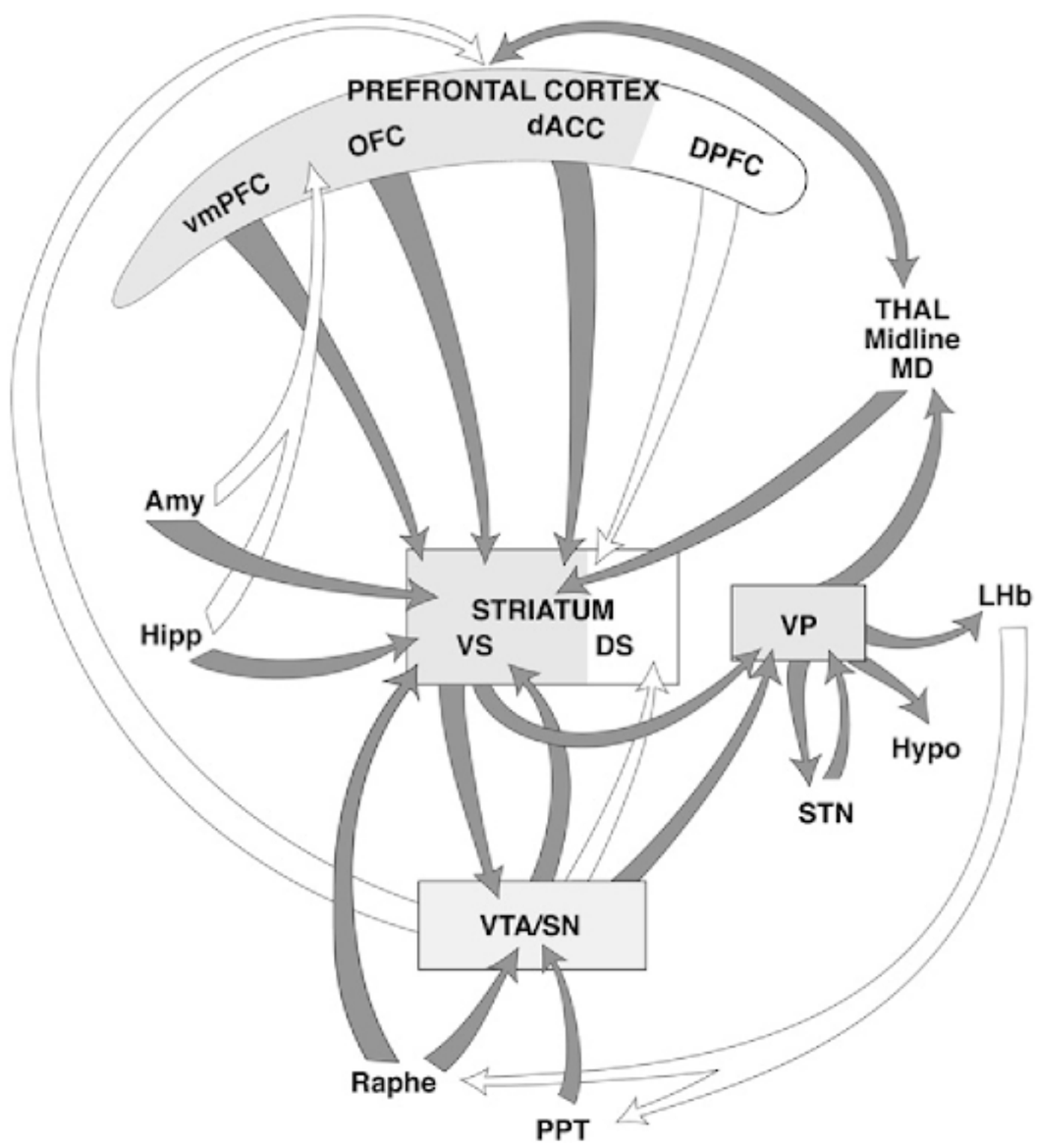

FIGURE 1.1 Schematic illustrating key structures and pathways of the reward circuit. *Shaded areas* and *gray arrows* represent the basic ventral cortical–basal ganglia structures and connections. *Amy*, amygdala; *dACC*, dorsal anterior cingulate cortex; *DPFC*, dorsal prefrontal cortex; *DS*, dorsal striatum; *Hipp*, hippocampus; *Hypo*, hypothalamus; *LHb*, lateral habenula; *MD*, mediodorsal nucleus of the thalamus; *OFC*, orbital frontal cortex; *PPT*, pedunculopontine nucleus; *SN*, substantia nigra pars compacta; *STN*, subthalamic nucleus; *THAL*, thalamus; *vmPFC*, ventral medial prefrontal cortex; *VP*, ventral pallidum; *VS*, ventral striatum; *VTA*, ventral tegmental area.

PREFRONTAL CORTEX

Although cells throughout the cortex fire in response to various aspects of reward processing, the main components of evaluating reward value and outcome are the orbital (OFC) and anterior cingulate (ACC) prefrontal cortices. These regions comprise several specific cortical areas: the orbital cortex is divided into areas 11, 12, 13, 14, and, often, caudal regions referred to as either parts of the insular cortex or periallo- and proisocortical areas; the ACC is divided into dorsal and subgenual regions, areas 24, 25, and 32 [9,10]. Based on specific roles for mediating different aspects of reward processing and emotional regulation, these regions can be functionally grouped into: (1) the OFC; (2) the ventral medial prefrontal cortex (VMPFC), which includes medial OFC and subgenual ACC; and (3) the dorsal ACC (DACC). In addition to the DACC, OFC, and VMPFC, the DPFC, in particular, areas 9 and 46, are engaged when working memory is required for monitoring incentive-based behavioral responses. The DPFC also encodes reward amount and becomes active when anticipated rewards signal future outcomes [11,12].

A key function of the OFC is to link sensory representations of stimuli to outcomes, which is consistent with its connections to both sensory and reward-related regions [12–15]. The OFC can be generally parceled into somewhat functionally different regions based on a caudal–rostral axis, with more caudal regions receiving stronger inputs from primary sensory areas and rostral regions connected to highly processed sensory areas. The OFC's unique access to both primary and highly processed sensory information, coupled with connections to the amygdala and cingulate, explains many of the functional properties of the region. Indeed, the two cardinal tests of OFC function are reward devaluation paradigms and stimulus-outcome reversal learning [16–18], both of which have been demonstrated with OFC lesions across species. Consistent with connectional differences between caudal and rostral OFC, there is an apparent gradient between primary reward representations in more caudal OFC/insular cortex and representations of secondary rewards such as money in more rostral OFC regions [19]. Such dissociations may rely on the differential inputs from early versus higher sensory representations to caudal versus rostral and OFC, respectively, or amygdala connections to caudal OFC and dorsolateral prefrontal cortex and a frontal pole to rostral OFC.

In contrast to the OFC, the ACC has a relative absence of sensory connections, but contains within in it a representation of many diverse frontal lobe functions, including motivation cognition and motor control, which is reflected in its widespread connections with other limbic, cognitive, and motor cortical areas. This

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is a complex area, but the overall role of the ACC appears to be involved in monitoring these functions for action selection [20–22]. Overall, the ACC can be divided functionally along its dorsal–ventral axis. The ventral ACC (areas 25 and ventral parts of 32) is closely associated with visceral and emotional functions and has strong connections to the hypothalamus, amygdala, and hippocampus. From a functional perspective, imaging and lesion studies have identified an area referred to as the VMPFC. Depending on the specific study, this region may include different combinations of these regions, but overall involves area 25, parts of 32, medial OFC (area 14 and 11), and ventromedial area 10. VMPFC cells track values in the context of internally generated states such as satiety [23]. Moreover, this area plays a role, not only in the valuation of stimuli, but also in selecting between these values. However, perhaps the most remarkable feature of the VMPFC valuation signal is its flexibility. Whereas several other brain regions rely on experience to estimate values, the VMPFC can encode values that must be computed quickly often just prior to, or during, an action [24].

The DACC, primarily area 24, is tightly linked with many PFC areas, including lateral regions associated with cognitive control, and more caudally, with motor control areas. Thus, the DACC sits at the connectional intersection of the brain's reward and action networks. Unlike OFC lesions, DACC lesions have little effect on learning reward reversals based on sensory cues, but they do if the rewards are tied to two different actions (such as "turn" or "push") [25,26]. Imaging studies show ACC activation in a wide variety of tasks, many of which can be explained in the context of selecting between different actions [27].

Anatomical relationships both within and between these PFC regions are complex. As such, several organizational schemes have been proposed based on combinations of cortical architecture and connectivity [6,9,10,28]. In general, cortical areas within each prefrontal group are highly interconnected. However, these connections are quite specific in that a circumscribed region within each area projects to specific regions of other areas, but not throughout. For example, a given part of area 25 of the VMPFC projects to only specific parts of area 14. Overall the VMPFC is primarily interconnected to other medial subgenual regions and to the DACC, with few connections to areas 9 and 46. In contrast, the DACC is tightly linked to area 9 and pre- and supplementary motor cortices. Different OFC regions are highly interconnected, but as with the VMPFC, these are specific connections. For example, not all of area 11 projects throughout area 13. Lateral OFC is connected to parts of the ventrolateral PFC. DPFC regions are interconnected and also project to the DACC, lateral OFC, area 8, and rostral premotor regions.

Finally, the VMPFC, OFC, and DACC are linked to the amygdala [29–31]. These projections arise primarily from the basal and lateral nuclear complex and terminate in specific regions along the ventral and medial cortical surface (VMPFC, OFC, and DACC). Few projections reach the lateral surfaces, although there are some dense terminals in the ventrolateral PFC. The amygdalocortical projections are bidirectional. Here, the OFC–amygdalar projections target the intercalated masses, whereas terminals from the VMPFC and DACC are more diffuse. An important additional connection primarily to the VMPFC, but also to parts of the OFC, is derived from the hippocampus. In contrast, there are few hippocampal projections to DACC or the dorsal and lateral PFC areas.

THE VENTRAL STRIATUM

The link between the nucleus accumbens and reward was first demonstrated as part of the self-stimulation circuit originally described by Olds and Milner [32]. Since then, the nucleus accumbens (and the VS in general) has been a central site for studying reward and drug reinforcement and for the transition between drug use as a reward and habit [33,34]. The term VS, coined by Heimer, includes the nucleus accumbens and the broad continuity between the caudate nucleus and putamen ventral to the rostral internal capsule, the olfactory tubercle, and the rostrolateral portion of the anterior perforated space adjacent to the lateral olfactory tract in primates [35]. From a connectional perspective, it also includes the medial caudate nucleus, rostral to the anterior commissure [36] (see later).

Human imaging studies demonstrate the involvement of the VS in reward prediction and reward prediction errors [37,38] and, consistent with physiological results in nonhuman primate studies, the region is activated during reward anticipation [39] (also see Fig. 4.1). Interestingly, the relative size of the cortical input to the nucleus accumbens compared against the size of hippocampal/amygdala nucleus accumbens projections predicts subjects' relative propensity for reward-seeking versus novelty-seeking behavior [40]. The VS blood oxygen level-dependent signal is regularly found to code for a reward prediction error [41,42]: the reward minus the expectation of that reward. It has been suggested that this signal depends on dopaminergic input, as DA cells are known for a similar pattern of reward coding [43], but other VS-projecting regions discussed earlier also code for rewards. It is therefore likely that the VS signal contains several combined reward representations. Such an idea is supported by data in which connectional and functional data were acquired in the same subjects. The extent to which the VS signal looks like a reward prediction error, rather than a simple coding of reward, depends on

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the strength of connection (measured by diffusion MRI tractography) between the VS and the dopaminergic midbrain [44]. Collectively, these studies demonstrate its key role in the acquisition and development of reward-based behaviors and its involvement in drug addiction and drug-seeking behaviors. However, it has been recognized for some time now that cells in the primate dorsal striatum as well as the VS respond to the anticipation, magnitude, and delivery of reward [45–47]. The striatum, as a whole, is the main input structure of the BG and receives a massive and topographic input from cerebral cortex (and thalamus). These afferent projections to the striatum terminate in a general topographic manner, such that the ventromedial striatum receives input from the VMPFC, OFC, and DACC; the central striatum receives input from the DPFC, including areas 9 and 46. Indeed, the different prefrontal cortical areas have corresponding striatal regions that are involved in various aspects of reward evaluation and incentive-based learning [38,48,49] and are associated with pathological risk-taking and addictive behaviors [50,51].

Special Features of the Ventral Striatum

While the VS is similar to the dorsal striatum in most respects, there are also some unique features. The VS contains a subterritory, called the shell, which plays a particularly important role in the circuitry underlying goal-directed behaviors, behavioral sensitization, and changes in affective states [52,53]. Whereas several transmitter and receptor distribution patterns distinguish the shell/core subterritories, calbindin is the most consistent marker for the shell across species [54]. Although a calbindin-poor region marks the subterritory of the shell, staining intensity of other histochemical markers in the shell distinguish it from the rest of the VS. In general, GluR1, GAP-43, acetylcholinesterase, serotonin, and substance P are particularly rich in the shell, while the μ receptor is relatively low in the shell compared to the rest of the striatum [55–58]. (Fig. 1.2A). Finally, the shell has some unique connectivities compared to the rest of the VS. These are indicated in the following.

In addition to the shell compartment, several other characteristics are unique to the VS. The DA transporter is relatively low throughout the VS including the core. This pattern is consistent with the fact that the dorsal tier DA neurons express relatively low levels of mRNA for the DA transporter compared to the ventral tier [59] (see later regarding the substantia nigra). In addition, unlike the dorsal striatum, the VS contains numerous cell islands, including the islands of Calleja, which are thought to contain quiescent immature cells that remain in the adult brain [60–62]. The VS also contains many pallidal elements that invade this ventral territory (see later regarding the VP). Of particular importance is the fact that, whereas both the dorsal and the ventral striatum receive input from the cortex, thalamus, and brain stem, the VS alone also receives a dense projection from the amygdala and hippocampus (Fig. 1.1). While collectively these are important distinguishing features of the VS, its dorsal and lateral border is continuous with the rest of the striatum and neither cytoarchitectonic nor histochemical distinctions mark a clear boundary between it and the dorsal striatum. Moreover, because reward-related cells are found throughout a large region of the rostral striatum, the best way to outline where this function lies is by its afferent projections from cortical areas that mediate different aspects of reward processing, the VMPFC, OFC, and DACC. Thus, in the following sections, we refer to the VS as that area of the striatum that receives inputs from these cortical regions. Note that this expands the traditional boundaries of the VS into the dorsomedial striatum.

Connections of the Ventral Striatum (See Fig. 1.3)

The VS is the main input structure of the ventral BG. Like the dorsal striatum, afferent projections to the VS are derived from three major sources: a massive, generally topographic input from the cerebral cortex; a large input from the thalamus; and a smaller, but critical input from the brain stem, primarily from the midbrain dopaminergic cells. The traditional way of viewing the overall organization of corticostriatal projections was to divide the striatum into the VS, input from limbic areas; the central striatum, input from associative cortical areas; and the dorsolateral striatum, input from sensorimotor areas [36,63]. However, as indicated above, the striatal region receiving input from reward-related areas expands outside of the traditional boundaries of the VS.

Cortical Projections to the Ventral Striatum

Corticostriatal terminals are organized in densely distributed patches [6,64,65] (Fig. 1.2B), which can be visualized at relatively low magnification. The overall general distribution of terminals from different cortical regions, viewed separately or in selective groupings, is the foundation for the concept of parallel and segregated cortical–BG circuits. However, as described in more detail later, the collective distribution of cortical inputs from different cortical areas demonstrates extensive converge of cortical terminals throughout the striatum, creating a complex interface between inputs from functionally distinct cortical regions. Indeed, each cortical region, while projecting topographically to the striatum, does not maintain the narrow funneling that

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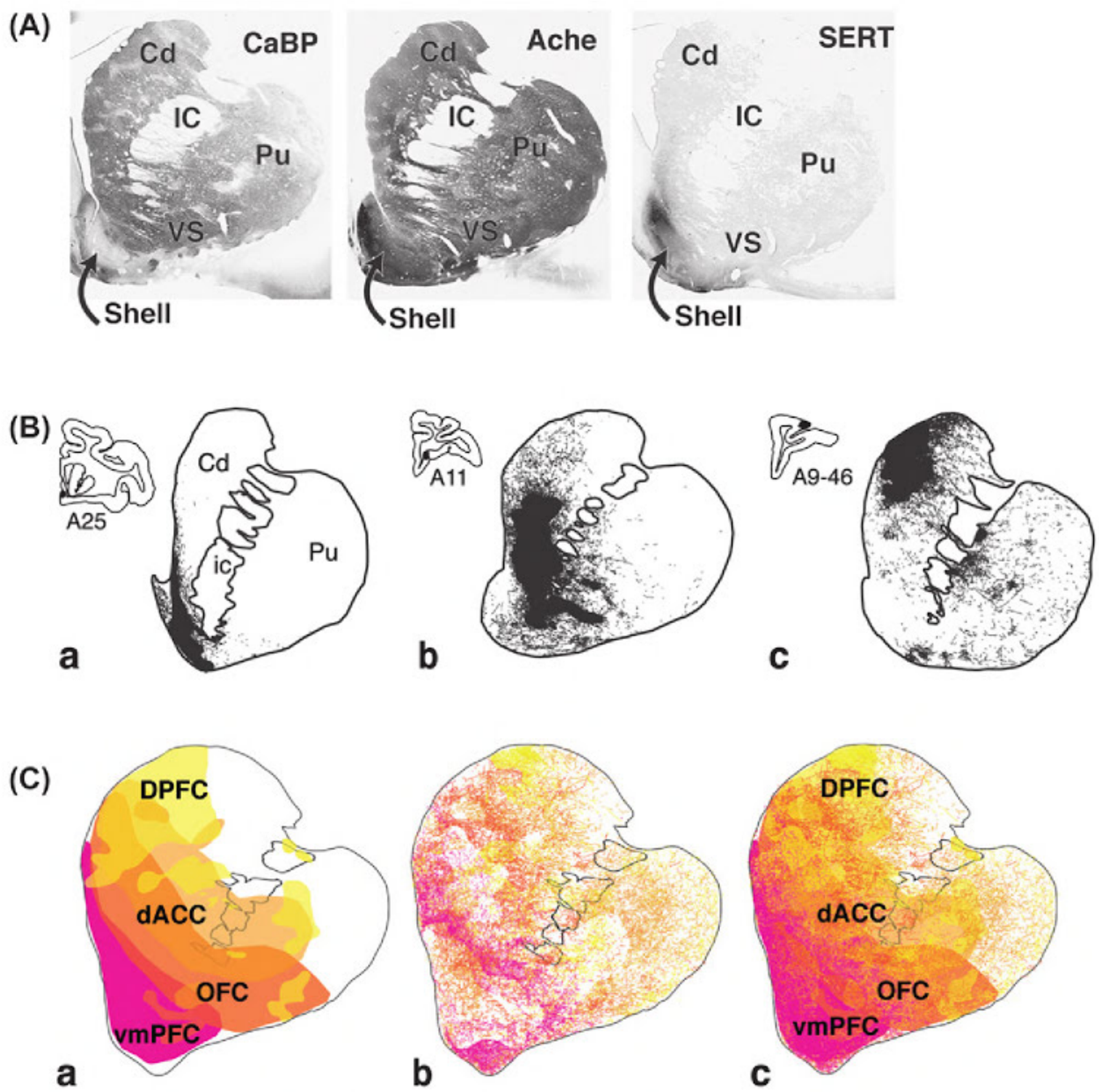

FIGURE 1.2 Histochemistry and connections of the rostral striatum. (A) Photomicrographs of the rostral striatum stained with three different histochemical markers to illustrate the shell: calbindin (*CaBP*), acetylcholinesterase (*Ache*), and serotonin (*SERT*). *Cd*, caudate nucleus; *IC*, internal capsule; *Pu*, putamen; *VS*, ventral striatum. (B) Schematic chartings of labeled fibers following injections into various prefrontal regions. (a) VMPFC injection site (area 25); (b) OFC injection site (area 11); (c) DPFC injection site (area 9/46). The dense projection fields are indicated in *solid black*. Note the diffuse projection fibers outside of the dense projection fields. (C) Schematics demonstrating convergence of cortical projections from various reward-related regions and dorsal prefrontal areas. (a) Convergence between dense projections from various prefrontal regions. (b) Distribution of diffuse fibers from various prefrontal regions. (c) Combination of dense and diffuse fibers. *dACC*, dorsal anterior cingulate cortex; *DPFC*, dorsal lateral prefrontal cortex; *OFC*, orbital prefrontal cortex; *vmPFC*, ventral medial prefrontal cortex. *Red*, inputs from vmPFC; *dark orange*, inputs from OFC; *light orange*, inputs from dACC; *yellow*, inputs from DPFC.

would be required to "fit" a large cortex into a far smaller striatal volume. For example, the volume occupied by the collective dense terminal fields from the VMPFC, DACC, and OFC is approximately 22% of the striatum, a larger cortical input than would be predicted by the relative cortical volume of these areas. Together, projections from these cortical areas terminate primarily in the rostral, medial, and ventral parts of the striatum and define the ventral striatal territory [6,66,67]. The large extent of this region is consistent with the findings that diverse striatal areas are activated following reward-related behavioral paradigms [51,68,69]. The dense projection field from the VMPFC is the most limited (particularly from area 25) and is concentrated within and just lateral to the shell (Fig. 1.2B(a)). The innervation of the shell receives the densest input from area 25, although fibers from areas 14 and 32 and from agranular insular cortex also terminate here. The VMPFC also projects to the medial wall of the caudate nucleus, adjacent to the ventricle. In contrast, the central and lateral parts of the VS (including the ventral caudate nucleus and putamen) receive inputs from the OFC (Fig. 1.2B(b)). These terminals also extend dorsally, along the medial caudate nucleus, but lateral to those from the VMPFC. There is some medial-to-lateral and rostral-to-caudal topographic organization of the OFC terminal fields. For example, projections from area 11 terminate rostral to those from area 13 and those from area 12 terminate laterally. Despite this general topography, overlap between the OFC terminals is significant. Projections from the DACC extend from the rostral pole of the

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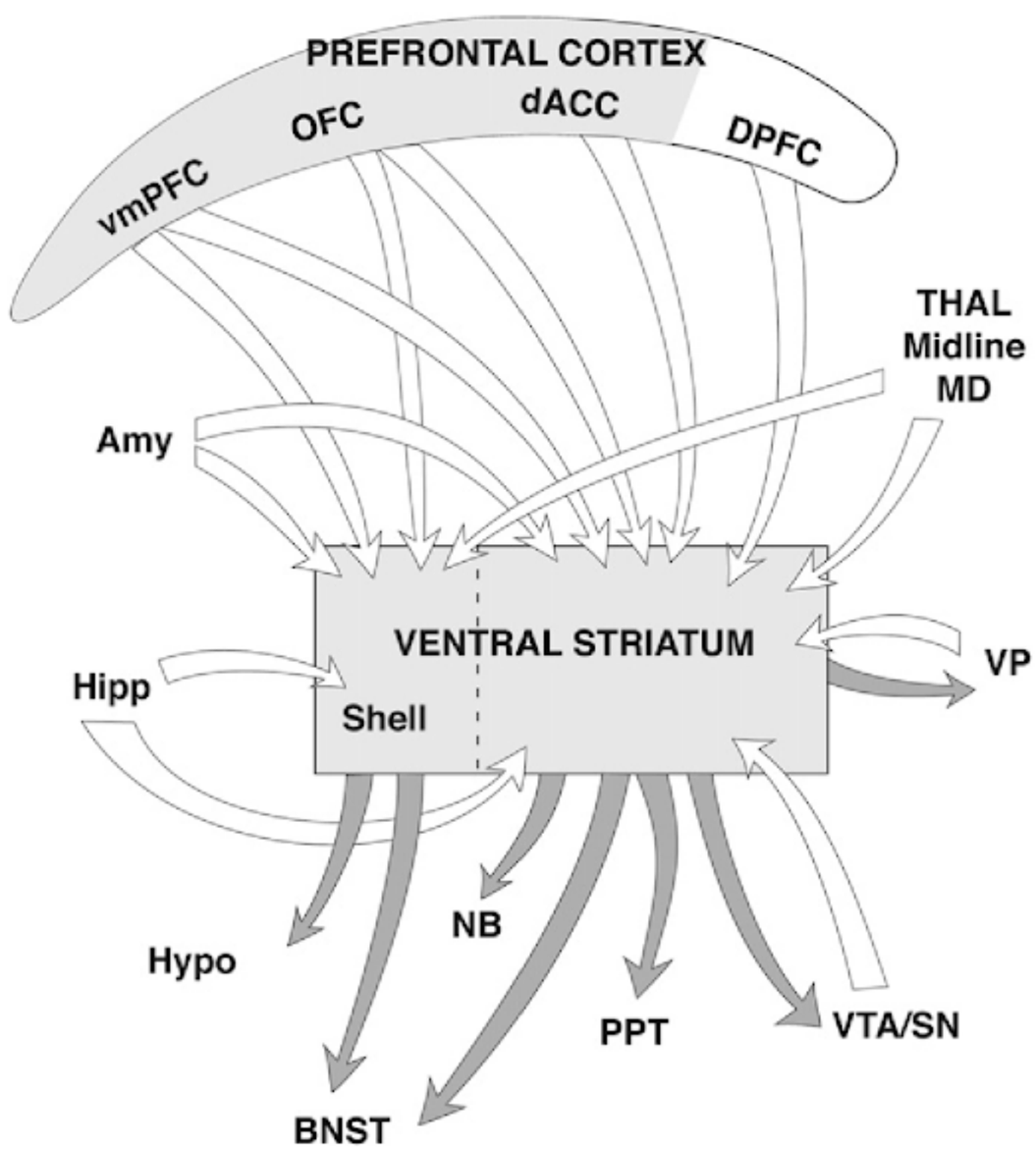

FIGURE 1.3 Schematic illustrating the connections of the ventral striatum. *White arrows*, inputs; *gray arrows*, outputs. *Amy*, amygdala; *BNST*, bed nucleus stria terminalis; *dACC*, dorsal anterior cingulate cortex; *DPFC*, dorsal lateral prefrontal cortex; *Hipp*, hippocampus; *Hypo*, hypothalamus; *MD*, mediodorsal nucleus of the thalamus; *OFC*, orbital frontal cortex; *PPT*, pedunculopontine nucleus; *SN*, substantia nigra pars compacta; *THAL*, thalamus; *vmPFC*, ventral medial prefrontal cortex; *VP*, ventral pallidum; *VTA*, ventral tegmental area.

striatum to the anterior commissure and are located in both the central caudate nucleus and the putamen. They primarily avoid the shell region. These fibers terminate somewhat lateral to those from the OFC. Thus, the OFC terminal fields are positioned between the VMPFC and the DACC. In contrast, the DPFC projects primarily in the head of the caudate and part of the rostral putamen (Fig. 1.2B(c)). Terminals from areas 9 and 46 are somewhat topographically organized and extend from the rostral pole, through the rostral, central putamen and much of the length of the caudate nucleus [6,65].

Despite the general topography described above, dense terminal fields from the VMPFC, OFC, and DACC show a complex interweaving and convergence, providing an anatomical substrate for modulation between circuits [6,7] (Fig. 1.2C). Dense projections from the DACC and OFC regions do not occupy completely separate territories in any part of the striatum, but converge most extensively at rostral levels. By contrast, there is greater separation of projections between terminals from the VMPFC and the DACC/OFC, particularly at caudal levels. These regions of convergence between the dense terminal fields of the VMPFC, OFC, and DACC provide an anatomical substrate for integration between reward-processing circuits within specific striatal areas and may represent critical "hubs" for integrating reward value, predictability, and salience.

In addition to convergence between VMPFC, DACC, and OFC dense terminals, projections from DACC and OFC also converge with inputs from the DPFC, demonstrating that functionally diverse PFC projections also converge in the striatum. At rostral levels, DPFC terminals converge with those from both the DACC and OFC, although each cortical projection also occupies its own territory. Here, projections from all PFC areas occupy a central region, the different cortical projection extending into nonoverlapping zones. Convergence is less prominent caudally, with almost complete separation of the dense terminals from the DPFC and DACC/OFC just rostral to the anterior commissure. Importantly, convergence does not take place only at the boundaries or edges of different functional domains. Rather, there are dense clusters of invading terminals from, for example, the DPFC, embedded deep within the dense projection field of the OFC. Because medium spiny neurons have a dendritic field spanning 0.5 mm [70], the area of convergence is likely to be larger than estimated based solely on the relationship between the afferent projections.

Using a computational model to characterize the consistency of cortical projection zones into the striatum predicts striatal locations that receive specific cortical inputs. These computations demonstrate that there is an exponential decay in overlap as a function of distance [7]. Thus, convergence of corticostriatal terminals from cortical areas that are separated by 5 mm is 50% in nonhuman primates. This overlap decreased to <20% from regions separated by 30 mm. This distance between cortical regions can span several functional domains. For example, there is a region within the rostral, anterior striatum that receives projections from across the prefrontal cortical regions, including the VMPFC, OFC, DACC, and dorsal and lateral PFC.

There has been growing interest in the idea of broad associative cortical networks, which feature nodes (or connection hubs) that integrate and distribute information across multiple systems [71,72]. These studies indicate that there are specific regions that receive inputs from multiple cortical areas that cross-link between functional systems. The aforementioned data suggest that these hubs exist in the striatum as well as the cortex. In particular, this rostral striatal region may serve as a hub for VMPFC, OFC, and DACC to connect with dorsal and lateral PFC regions that integrates motivational, reward, and cognitive control information. It is possible that this convergence of cortical areas on specific locations in the striatum may thus facilitate value

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computations across diverse domains into a common currency. Thus, a coordinated activation of DPFC, DACC, and/or OFC terminals in specific striatal regions would produce a unique combinatorial activation at the specific sites suggesting specific subregions for reward-based incentive drive to influence long-term strategic planning and habit formation. In contrast to this, some striatal regions, particularly posterior and lateral portions, receive inputs from only a few prefrontal regions, and therefore they may serve more specialized computational roles.

The Amygdala and Hippocampal Projections to the Ventral Striatum

The amygdala is a prominent limbic structure that plays a key role in the emotional coding of environmental stimuli and provides contextual information used for adjusting motivational level that is based on immediate goals. It comprises the basolateral nuclear group (BLNG), the corticomedial region, and the central amygdaloid complex. The BLNG, the primary source of amygdaloid input to the VS outside the shell, processes higher order sensory inputs in all modalities except olfactory, and responds to highly palatable foods and "multimodal" cues. Overall, the basal nucleus and the magnocellular division of the accessory basal nucleus are the main sources of inputs to the VS [73,74]. The lateral nucleus has a relatively minor input to the VS. The amygdala has few inputs to the dorsal striatum in primates. The basal and accessory basal nuclei innervate both the shell and the ventromedial striatum outside the shell. Moreover, there is a topographic organization to that innervation, such that inputs from basal nucleus subdivisions target different regions of the VS. The shell is set apart from the rest of the VS by a specific set of connections derived from the medial part of the central nucleus, periamygdaloid cortex, and medial nucleus of the amygdala. Thus, much like the topography of prefrontal inputs to the VS, nuclei of the amygdala that mediate various functions target subterritories of the ventromedial striatum. In contrast to the amygdala, the hippocampal formation projects to a more limited region of the VS. The main terminal field is located in the most medial and ventral parts of the VS, essentially confined to the shell region. However, additional fibers do extend outside the boundary of the shell. The subiculum appears to provide the main source of this input. Moreover, some afferent fibers are also derived from the parasubiculum and part of CA1 [75]. Inputs from both the hippocampus and the amygdala terminate in overlapping regions of the shell [75,76].

Thalamic Projections to the Ventral Striatum

The midline and medial intralaminar thalamic nuclei project to medial prefrontal areas, the amygdala, and hippocampus and, as such, are considered the limbic-related thalamic nuclear groups. The VS receives dense projections from the midline thalamic nuclei and from the medial parafascicular nucleus [77,78]. The midline nuclei include the anterior and posterior paraventricular, paratenial, rhomboid, and reuniens thalamic nuclei. The shell of the nucleus accumbens receives the most limited projection. The medial shell is innervated almost exclusively by the anterior and posterior paraventricular nuclei and the medial parafascicular nucleus. The ventral shell receives input from these nuclei as well as from the paratenial, rhomboid, and reuniens midline groups. The medial wall of the caudate nucleus receives projections, not only from the midline and the medial intralaminar nuclei, but also from the central superior lateral nucleus. In contrast, the central part of the VS receives a limited projection from the midline thalamic nuclei, predominantly from the rhomboid nucleus. It also receives input from the parafascicular nucleus and the central superior lateral nucleus. In addition to the midline and intralaminar thalamostriatal projections, in primates there is a large input from the "specific" thalamic BG relay nuclei, the medial dorsalis nucleus (MD) and ventral anterior and ventral lateral nuclei [79,80]. The VS also receives these direct afferent projections, which are derived primarily from the MD and a limited input from the magnocellular subdivision of the ventral anterior nucleus.

Efferent Projections From the Ventral Striatum (See Fig. 1.4)

Efferent projections from the ventral striatum, like those from the dorsal striatum, project primarily to the pallidum and substantia nigra/VTA [81,82]. Specifically, they terminate topographically in the subcommissural part of the globus pallidus (classically defined as the VP), the rostral pole of the external segment, and the rostromedial portion of the internal segment. The more central and caudal portions of the globus pallidus do not receive this input. Fibers from the VS projecting to the substantia nigra are not as confined to a specific region as those projecting to the globus pallidus. Although the densest terminal fields occur in the medial portion, numerous fibers also extend laterally to innervate the dorsal tier of the midbrain dopaminergic neurons (see section on the substantia nigra). This projection extends throughout the rostral–caudal extent of the substantia nigra. Projections from the medial part of the VS also project more caudally, terminating in the pedunculopontine nucleus and, to some extent, in the medial central gray. In addition to projections to the typical BG output structures, the VS also projects to non-BG regions. The shell sends fibers caudally and medially into the lateral hypothalamus. Axons from the medial VS (including the shell) travel to and terminate in the bed nucleus of

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the stria terminalis and parts of the ventral regions of the VS terminate in the nucleus basalis [81]. A projection to the nucleus basalis in the basal forebrain is of particular interest, because this is the main source of cholinergic fibers to the cerebral cortex and the amygdala. These data indicate that the VS may influence the cortex directly, without going through the pallidal, thalamic circuit. A potential connection between ventral striatal fibers and cholinergic neurons in the basal forebrain has been demonstrated at the light microscopic level in several species, including primates, and verified at the electron microscope level and, more recently, using optogenetic methods in rodents [83–88]. Likewise, the projection to the bed nucleus of the stria terminalis indicates direct striatal influence on the extended amygdala.

VENTRAL PALLIDUM (FIG. 1.4)

The VP is an important component of the reward circuit. These cells respond specifically during the learning and performance of reward-incentive behaviors and are an area of focus in the study of addictive behaviors [89,90]. The VP, like the dorsal pallidum, has indirect (via the medial STN and adjacent hypothalamus) and direct projections to the MD thalamus, thus completing the loop back to the cortex [91]. The STN connection with the VP, along with a hyperdirect pathway from the VMPFC, OFC, and ACC to the medial STN, highlights the role of the STN in the reward pathway [8,91]. This will be discussed in more detail later. Pallidal cells, including the VP, send direct input to the LHb [91,92]. The LHb, in turn, projects indirectly to the DA cells. Thus, the VP, STN, and LHb are important

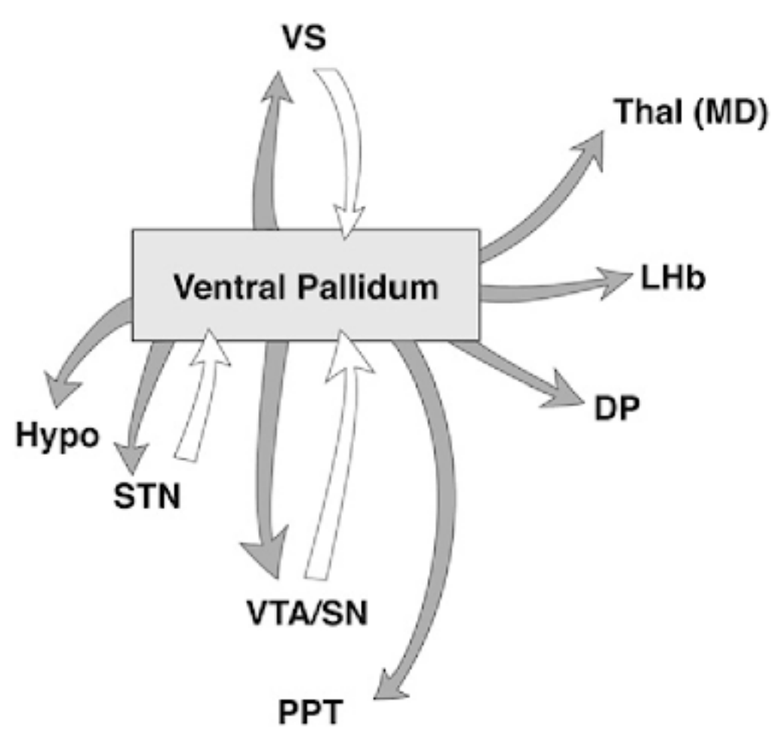

FIGURE 1.4 Schematic illustrating the connections of the ventral pallidum. *DP*, dorsal pallidum; *Hypo*, hypothalamus; *LHb*, lateral habenula; *MD*, mediodorsal nucleus of the thalamus; *PPT*, pedunculopontine nucleus; *SN*, substantia nigra; *STN*, subthalamic nucleus; *Thal*, thalamus; *VS*, ventral striatum; *VTA*, ventral tegmental area.

components of the reward circuit. VP cells respond specifically during the learning and performance of reward-incentive behaviors. The complexity of the VP circuitry coupled with its central position in the reward circuit indicates that this structure is likely to be activated during imaging studies. Neuroimaging studies that document ventral striatal activation often document overlapping ventral pallidal activation. However, the lack of sufficient spatial resolution makes it difficult to distinguish the VP from the VS. LHb cells are inhibited by a reward-predicting stimulus, but fire following a nonreward signal. This stimulation of the LHb directly or following a nonreward signal inhibits DA cells [93,94]. Interestingly, few fibers from the LHb directly reach the SNc in primates; rather these cells project primarily to the rostromedial tegmental nucleus (RMTg), which, in turns projects to DA cells. An event-related fMRI study featuring adequate spatial and temporal resolution to visualize habenular activity indicated that negative but not positive feedback activates the habenular complex, consistent with findings from nonhuman primate electrophysiology [95].

The term VP was first used to describe in rats the region below the anterior commissure, extending into the anterior perforated space, based both on histological criteria and on its input from the then defined VS [96]. However, in primates, it is best defined by its input from the entire input from reward-related VS. As indicated earlier, that would include not only the subcommissural regions, but also the rostral pole of the external segment and the medial rostral internal segment of the globus pallidus. Like the dorsal pallidum, the VP contains two parts: a substance-P-positive and enkephalin-positive component, which project to the thalamus and STN, respectively [91,97–99]. Pallidal neurons have a distinct morphology that is outlined with immunoreactivity for these peptides, making these stains particularly useful for determining the boundaries and extent of the VP [99–103]. These fibers, which appear as tubular-like structures, referred to as "wooly fibers," demonstrate the extent of the VP and its continuity with the dorsal pallidum [102]. The VP reaches not only ventrally, but also rostrally to invade the rostral and ventral portions of the VS, sending finger-like extensions into the anterior perforated space. In the human brain the VP extends far into the anterior perforated space, where the structure appears to be rapidly broken up into an interconnected lacework of pallidal areas, interdigitating with striatal cell islands and microcellular islands, including possibly the deep islands of Calleja. The identification of the VP and VS simplified the structural analysis of the ventral forebrain, demonstrating that a large part of the area referred to as "substantia innominata" is actually an extension of the reward-related

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striatopallidal complex [55]. In addition to the GABAergic ventral striatal input, there is a glutamatergic input from the STN nucleus and a dopaminergic input from the midbrain [104,105].

Descending efferent projection from the VP terminates primarily in the medial STN, extending into the adjacent lateral hypothalamus [91,106–108]. Axons continue into the substantia nigra, terminating medially in the SNc, substantia nigra pars reticulata (SNr), and VTA. Projections from the VP to the STN and the lateral hypothalamus are topographically arranged. This arrangement demonstrates that pathways from distinct pallidal regions that receive specific striatal input terminate in specific subthalamic/hypothalamic regions, thus maintaining a topographic arrangement. In contrast, terminating fibers from the VP in the substantia nigra overlap extensively, suggesting convergence of terminals from different ventral pallidal regions. Fibers continue caudally to innervate the pedunculopontine nucleus. As with the dorsal pallidum, components of the VP project to the thalamus, terminating in the midline nuclei and medial MD nucleus. Pallidal fibers entering the thalamus give off several collaterals that form branches that terminate primarily onto the soma and proximal dendrites of thalamic projection cells. In addition, some synaptic contact is also made with local circuit neurons. This terminal organization indicates that, while pallidal projections to the thalamus are primarily inhibitory on thalamic relay neuron cells, they may also function to disinhibit projection cells via the local circuit neurons [109,110]. In addition, the VP also projects to both the internal and the external segments of the dorsal pallidum. This is a unique projection, in that the dorsal pallidum does not seem to project ventrally.

Parts of the VP (along with the dorsal pallidum) project to the LHb nucleus. Most cells that project here are located in the region that circumvents the internal segment and, in particular, are embedded within the accessory medullary lamina that divides the lateral and medial portions of the dorsal internal segment project [106,111]. Finally, part of the ventral pallidal area [as with the external segment of the globus pallidus (GPe)] also projects to the striatum [112]. This pallidostriatal pathway is extensive in the monkey and is organized in a topographic manner preserving a general, but not strict, medial-to-lateral and ventral-to-dorsal organization. The terminal field is widespread and nonadjacent pallidal regions send fibers to the striatum that overlap considerably indicating convergence of terminals from different pallidal regions. Thus, the pallidostriatal pathway contains both a reciprocal and a nonreciprocal pathway. The nonreciprocal component suggests that this feedback projection may play an additional role in integrating information between ventral striatal subcircuits.

THE MIDBRAIN DOPAMINE NEURONS

DA neurons play a central role in the reward circuit [43,113]. While behavioral and pharmacological studies of DA pathways have led to the association of the mesolimbic pathway and nigrostriatal pathway with reward and motor activity, respectively, more recently both of these cell groups have been associated with reward. The midbrain DA neurons project widely throughout the brain. However, studies of the rapid signaling that is associated with incentive learning and habit formation focus on the DA striatal pathways.

The midbrain DA neurons are divided into the VTA and the SNc. Based on projection and chemical signatures, these cells are also referred to as the dorsal and ventral tier neurons [59] (Fig. 1.5A). The dorsal tier includes the VTA and the dorsal part of the SNc (also referred to as the retrorubral cell group). The cells of the dorsal tier are calbindin positive and contain relatively low levels of mRNA for the DA transporter and D2 receptor subtype. They project to the VS, cortex, hypothalamus, and amygdala. The ventral tier of DA cells are calbindin negative, have relatively high levels of mRNA for the DA transporter and D2 receptor, and project primarily to the dorsal striatum. Ventral tier cells (calbindin poor, DA transporter and D2 receptor rich) are

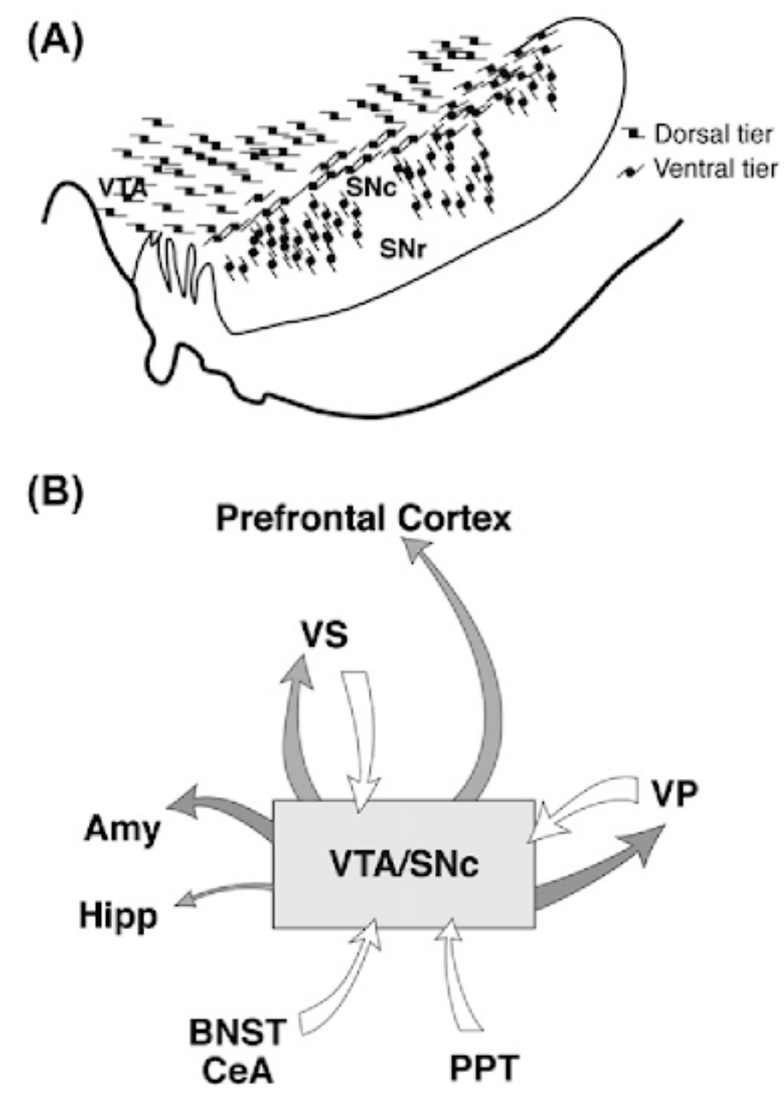

FIGURE 1.5 Schematic illustrating the (A) organization and (B) connections of the midbrain dopamine cells. *Amy*, amygdala; *BNST*, bed nucleus stria terminalis; *CeA*, central amygdala nucleus; *Hipp*, hippocampus; *PPT*, pedunculopontine nucleus; *SNc*, substantia nigra pars compacta; *SNr*, substantia nigra pars reticulata; *VP*, ventral pallidum; *VS*, ventral striatum; *VTA*, ventral tegmental area.

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more vulnerable to degeneration in Parkinson's disease and to *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced toxicity, whereas the dorsal tier cells are selectively spared [114]. As mentioned before, despite these distinctions, both cell groups respond to unexpected rewards.

Afferent Projections (Fig. 1.5B)

Input to the midbrain DA neurons is primarily from the striatum, from both the GPe and the VP, and from the brain stem. In addition, there are projections to the dorsal tier from the bed nucleus of the stria terminalis, the sublenticular substantia innominata, and the extended amygdala (the bed nucleus of the stria terminalis and the central amygdala nucleus).

As described earlier, the striatonigral projection is the most massive projection to the SN and terminates in both the VTA/SNc and the SNr [115–118]. The ventral (like the dorsal) striatonigral connection terminates throughout the rostrocaudal extent of the substantia nigra. There is an inverse ventral/dorsal topography to the striatonigral projections. The dorsolateral striatonigral inputs are concentrated in the ventrolateral SN. These striatal cells project primarily to the SNr, but also terminate on the cell columns of DA neurons that penetrate deep into the SNr. In contrast, the ventral striatonigral inputs terminate in the VTA, the dorsal part of the ventral tier, and in the medial and dorsal SNr. Thus the VS not only projects throughout the rostrocaudal extent of the substantia nigra, but also covers a wide mediolateral range [5,118].

Descending projections from the central nucleus of the amygdala also terminate in a wide mediolateral region, but are limited primarily to the dorsal tier cells. In addition, there are projections to the dorsal tier from the bed nucleus of the stria terminalis and from the sublenticular substantia innominata that travel together with those from the amygdala [119,120]. Both the GPe and the VP project to the substantia nigra. The pallidal projection follows an inverse dorsal/ventral organization similar to that of the striatonigral projection. Thus, the VP projects dorsally, primarily to the dorsal tier and dorsal SNc. The pedunculopontine nucleus sends a major glutamatergic input to the dopaminergic cell bodies. In addition, there is a serotonergic innervation from the dorsal raphe nucleus, though there is disagreement regarding whether fibers terminate primarily in the pars compacta or pars reticulata. Other brain-stem inputs to the DA neurons include those from the superior colliculus, the parabrachial nucleus, and the locus coeruleus. These inputs raise the interesting possibility that DA cells receive a direct sensory input. The collicular input, in particular, has been suggested to be responsible for the short-latency burst-firing activity of the DA cells in response to a salient or rewarding stimuli [67]. Finally, in primates, there is a small and limited projection from the PFC to the midbrain DA neurons, to both the VTA and the SNc. While considerable attention has been given to this projection, relative to the density of its other inputs, it is weak in primates [121].

Efferent Projections (Fig. 1.5B)

The largest midbrain DA neuron efferent projection is to the striatum [116,117,122]. As with the descending striatonigral pathway, there is a mediolateral and an inverse dorsoventral topography arrangement to the projection. The ventral pars compacta neurons project to the dorsal striatum and the dorsally located DA neurons project to the VS. The shell region receives the most limited input, primarily derived from the medial VTA [122]. The rest of the VS receives input from the entire dorsal tier. In addition, there are some afferent projections from the medial region and dorsal part of the SNc. In contrast to the VS, the central striatal area (the region innervated by the DPFC) receives input from a wide region of the SNc. The dorsolateral (motor-related) striatum receives the largest midbrain projection from cells throughout the ventral tier. In contrast to the dorsolateral region of the striatum, the VS receives the most limited DA cell input. Thus, in addition to an inverse topography, there is also a differential ratio of DA projections to the various striatal areas [5].

The dorsal tier cells also project widely throughout the primate cortex and are found not only in granular areas but also in agranular frontal regions, parietal cortex, temporal cortex, and, albeit sparsely, in occipital cortex [123,124]. The majority of DA cortical projections are from the parabrachial pigmented nucleus of the VTA and the dorsal part of the SNc. The VTA also projects to the hippocampus, albeit to a lesser extent than in neocortex. The DA cells that project to functionally different cortical regions are intermingled with one another, in that individual neurons send collateral axons to different cortical regions. Thus the nigrocortical projection is a more diffuse system compared to the nigrostriatal system, and can modulate cortical activity at several levels. DA fibers are located in superficial layers, including a prominent projection throughout layer I. This input provides a general modulation of cortical cells at the distal apical dendrites. DA fibers are also found in the deep layers in specific cortical areas [125,126]. Projections to the amygdala arise primarily from the dorsal tier. These terminals form symmetric synapses primarily with spiny cells of specific subpopulations in the amygdala [127]. As indicated earlier, DA fibers also project to the VP.

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The Striatonigrostriatal Network

While the role of DA in reward is well established, the latency between the presentation of the reward stimuli and the activity of the DA cells is too short to reflect higher cortical processing necessary for linking a stimulus with its rewarding properties. The fast, burst-firing activity is likely, therefore, to be generated from other inputs such as in brain-stem glutamatergic nuclei [67]. An interesting issue, then, is how do the DA cells receive information concerning reward value? The largest forebrain input to the DA neurons is from the striatum. However, this is a relatively slow GABAergic inhibitory projection, unlikely to result in the immediate, fast burst-firing activity. Nonetheless, the collective complex network of PFC, amygdala, and hippocampal inputs to the VS integrates information related to reward processing and memory to modulate striatal activity. These striatal cells then have a direct impact on a subset of medial DA neurons, which, through a series of connections described later, influences the dorsal striatum.

As mentioned before, projections from the striatum to the midbrain are arranged in an inverse dorsal–ventral topography and there is also an inverse dorsal–ventral topographic organization to the midbrain striatal projection. Considered separately, each limb of the system creates a loose topographic organization, the VTA and medial SN being associated with the limbic system, and the central and ventral SN with the associative and motor striatal regions, respectively. However, each functional region differs in their proportional projections, which significantly alter their relationship to one another. The VS receives a limited midbrain input, but projects to a large region. In contrast, the dorsolateral striatum receives a wide input, but projects to a limited region. In other words, the VS influences a wide range of DA neurons, but is itself influenced by a relatively limited group of DA cells. On the other hand, the dorsolateral striatum influences a limited midbrain region, but is affected by a relatively large midbrain region.

With this arrangement, while the VS receives input from the VMPFC, OFC, DACC, and amygdala, its efferent projection to the midbrain extends beyond the tight VS/dorsal tier DA/VS circuit. It terminates also in the ventral tier, to influence the dorsal striatum. Moreover, this part of the ventral tier is reciprocally connected to the central (or associative) striatum. The central striatum also projects to a more ventral region than it receives input from. This region, in turn, projects to the dorsolateral (or motor) striatum. Taken together, the interface between different striatal regions via the midbrain DA cells is organized in an ascending spiral interconnecting different functional regions of the striatum and creating a feed-forward organization, from reward-related regions of the striatum, to cognitive and motor areas (see Fig. 1.6). Thus, although the short-latency burst-firing activity of DA that signals immediate reinforcement is likely to be triggered from brain-stem nuclei, the corticostriato-midbrain pathway is in the position to influence DA cells to distinguish rewards and modify responses to incoming salient stimuli over time. This pathway is further reinforced via the nigrostriatal pathway, placing the striatonigrostriatal pathway in a pivotal position for transferring from the VS to the dorsal striatum during learning and habit formation. Indeed, cells in the dorsal striatum are progressively recruited during various types of learning, from simple motor tasks to drug self-administration [128–132]. Moreover, when the striatonigrostriatal circuit is interrupted, information transfer from Pavlovian to instrumental learning does not take place [133].

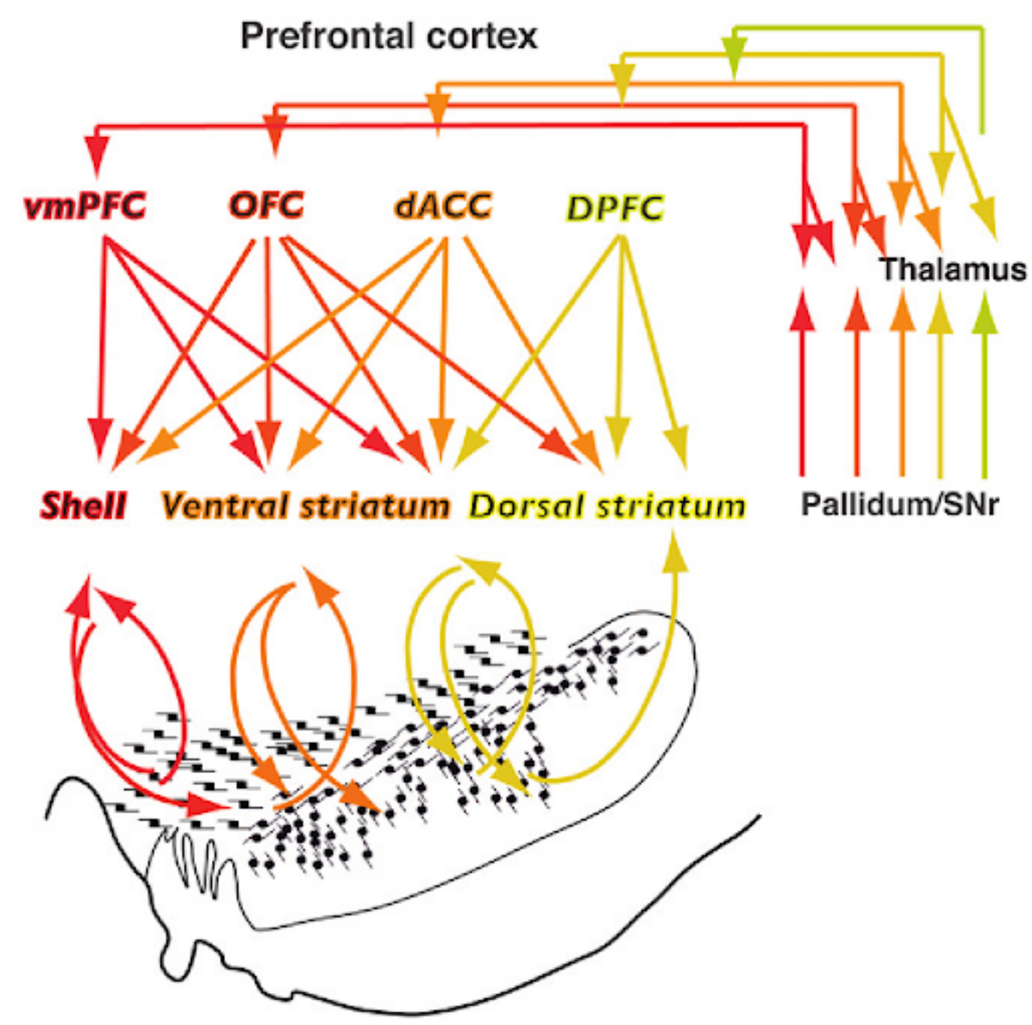

FIGURE 1.6 Three networks of integration through cortical–basal ganglia pathways. (1) Fibers from different prefrontal areas converge within subregions of the striatum. (2) Through the organization of striatonigrostriatal projections, the ventral striatum can influence the dorsal striatum [5]. Midbrain projections from the shell target both the VTA and the ventromedial SNc. Projections from the VTA to the shell form a "closed," reciprocal loop, but also project more laterally to impact on DA cells projecting to the rest of the ventral striatum forming the first part of a feed-forward loop (or spiral). The spiral continues through the striatonigrostriatal projections through which the ventral striatum impacts on cognitive and motor striatal areas via the midbrain DA cells. (3) The nonreciprocal corticothalamic projection carries information from reward-related regions, through cognitive and motor controls. *dACC*, dorsal anterior cingulate cortex; *DPFC*, dorsal prefrontal cortex; *OFC*, orbital prefrontal cortex; *SNr*, substantia nigra pars reticulata; *vmPFC*, ventral medial prefrontal cortex. *Red*, vmPFC pathways; *dark orange*, OFC pathways; *light orange*, dACC pathways; *yellow*, DPFC pathways; *green*, output to motor control areas.

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COMPLETING THE CORTICAL–BASAL GANGLIA REWARD CIRCUIT

In addition to the PFC, VS, VP, amygdala, and hippocampus, other key components of the circuit include the STN, the LHb, and the thalamus. Each of these structures has complex connectivities with multiple brain regions that we briefly review here.

Subthalamic Nucleus, the Hyperdirect Cortical Pathway

Like the corticostriatal connection, frontal areas project to or within the immediate region of the STN in a patchy manner and follow a general functional topography. Motor and premotor projections are concentrated in the lateral, dorsal, and caudal parts of the nucleus. In contrast, prefrontal projections are concentrated in the anterior, ventral, and medial half of the STN. Moreover, regions within the motor control areas and prefrontal cortex terminate in a topographic manner. For example, M1 projects to the dorsolateral STN and area 6 projects ventromedially to M1 projections [134–136]. Overall area 8 and caudal 9 and 46 terminals are located ventral and medial to premotor and motor projections [135]. Rostral areas 10, 9, and 46 terminate in the medial half of the STN [8]. DACC terminal fields are located medial to these projections in the anterior, medial tip of the STN. The location of the terminals from VMPFC/OFC and DACC are of particular interest here. Whereas DPFC dense projections are contained within the conventional medial border of the STN, DACC projections straddle this border and VMPFC/OFC terminals are located outside of it in the adjacent lateral hypothalamus (LH). Thus, the cone-shaped region that surrounds the ventromedial tip of the STN is occupied by VMPFC/OFC and part of the DACC projections. Indeed, the cortical terminal fields in this area are in the topographic continuity of the other PFC projections. Interestingly, terminals from and cells to the VP, a known STN input/output, are in the same location surrounding the medial tip of the STN [91]. Thus, the hyperdirect pathway defines a topographic anatomic connection, composed of a rostral limbic component, concentrated in the medial tip of the STN and the adjacent LH; a cognitive component in the medial half; and a more lateral and caudal motor component centered in the lateral half of the STN. This is consistent with the topography of the pallido-STN interconnection [91,137,138]. However, importantly, as seen with the corticostriatal projection, overlap between the various prefrontal projections is extensive, suggesting complex integration between these [8]. Thus, OFC and VMPFC terminals overlap with DACC dense terminals in the medial tip of the STN and the LH. DACC converges with DPFC. DPFC terminals also overlap with those from area 6.

Similar to the pallidum, the morphology of STN dendrites indicates that convergence between STN cortical inputs from different functional areas may be greater than it appears based on projection patterns. STN dendrites are oriented along the long axis of the nucleus and occupy approximately two-thirds of its volume [139]. Each dendrite stretches across multiple functional regions and receives inputs along this entire length. Indeed, inputs from the VP and globus pallidus have been shown to converge onto a single STN neuron [140]. Thus, STN neurons at the interface of functional territories are likely to receive convergent inputs onto their proximal dendrites.

The Lateral Habenula, a Negative-Reward Signal

The LHb also plays a central role in the reward circuit through its interaction with DA cells [93,95,141]. LHb cells fire following a nonreward signal and are inhibited by reward-predicting stimuli [93,142]. Stimulation of the LHb nuclei results in a negative-reward-related signal in the SNc [93]. Indeed, LHb firing is strongest when there is 0% probability of a reward or a 100% probability of an aversive outcome [143]. These cells project to and excite the GABAergic cells in the RMTg that, in turn, inhibits DA burst firing in response to reward, thus driving a negative reward signal [94,144–146]. The inputs to the LHb are primarily from the LH and globus pallidus, including, but not limited to the VP [147,148]. In primates, cells projecting to the LHb arise primarily from forebrain areas: the internal globus pallidus segment (GPi) and the limbic-related VP, the adjacent LH, and the perifornical area [91,92,148]. The GPi and VP receive indirect topographic input from prefrontal regions associated with reward value and reward learning via the striatum.

The Thalamus, the Final Link Back to Cortex

The MD and midline thalamic nucleus are a critical piece of the frontal–BG circuit that mediates reward, motivation, and emotional drive. As noted earlier, each PFC region of the frontal cortex is connected with specific areas of striatum, pallidum, and thalamus. The thalamus represents the final BG link and is often treated as a simple "one-way relay" back to cortex. The medial MD nucleus projects to the PFC, and is the final link in the reward circuit [91,149,150]. However, these connections are bidirectional. Moreover, while corticothalamic projections of the specific thalamic relay nuclei follow a general rule of reciprocity, the corticothalamic projections of the MD (as seen in other thalamocortical systems) are more extensive than its thalamocortical projections [150–152]. Importantly, they are, in part, derived from areas not innervated by the same thalamic region,

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indicating a nonreciprocal corticothalamic component. In particular, within the reward circuit, whereas the MD completes the reward cortical–BG circuit, its nonreciprocal input is derived from functionally distinct frontal cortical areas. For example, within the reward circuit, the central MD has reciprocal projections with the OFC, but also a nonreciprocal input from the VMPFC. More lateral MD areas are reciprocally connected to the DPFC, but also have a nonreciprocal connection to and from the OFC [150].

The Lateral Habenula, Pedunculopontine Tegmental Nucleus, and the Raphe Serotonergic Systems

Studies have emphasized the potential importance of the LHb in regulating the DA reward signal. In particular, experiments show that stimulation of the LHb nuclei in primates results in a negative-reward-related signal in the SNc, by inhibiting DA activity when an expected reward does not occur [93]. These LHb cells are inhibited by a reward-predicting stimulus, but fire following a nonreward signal. Stimulation of the LHb inhibits DA cells, suggesting that it plays a key role in regulating the DA reward (or rather negative reward) signal. Interestingly, few fibers from the LHb directly reach the SNc in primates, indicating an indirect regulation of the DA signal. There are several possible routes by which the LHb might impact on the DA cell. Connections described in rats, in addition to those to BG structures, include the basal forebrain, preoptic area of the hypothalamus, interpeduncular nucleus, pedunculopontine nucleus, raphe nucleus, superior colliculus, pretectal area, central gray, VTA, and reticular formation [91,145,147]. The pedunculopontine tegmental nucleus is connected to multiple BG structures and provides one of the strongest excitatory inputs to the midbrain DA cells [153,154]. Moreover, the cells in this brain-stem area receive input from the LHb. Anatomical and physiological studies, coupled with the central role of DA for reward prediction error, led to studies that support the hypothesis that the pedunculopontine nucleus may play a role in this reward signal [155]. The brain stem serotonergic system plays an important role in reinforcement behaviors by encoding expected and received rewards [156]. This reward signal could arise from a number of brain regions, but perhaps the strongest might arise from inputs derived from the OFC and VMPFC, the amygdala, the substantia nigra, and the LHb [157].

Complex Network Features of the Reward Circuit

The reward circuit comprises several cortical and subcortical regions that form a complex network to mediate different aspects of incentive learning, leading to adaptive behaviors and good decision-making. The cortical–BG network is at the center of this circuit. This complex network involves a system in which the PFC exploits the BG for additional processing of reward to effectively modulate learning that leads to the development of goal-directed behaviors and action plans. To develop an appropriate behavioral response to external environmental stimuli, information about motivation and reward needs to be combined with a strategy and an action plan for obtaining the goal. In other words, it is not sufficient to desire or want to, for example, to win at a card game. One has to understand the rules of the game, remember the cards played, etc., before executing the play. In addition, there is a complex interaction between the desire to put cards in play and the inhibition of impulse to play them too early. Thus action plans developed toward obtaining a goal require a combination of reward processing, cognition, and motor control. Yet, theories related to cortical–BG processing have emphasized the separation between functions (including different reward circuits), highlighting separate and parallel pathways [158–160]. The pathways and connections reviewed in this chapter clearly show that there are dual cortical–BG systems permitting both parallel and integrative processing.

Thus the reward circuit does not work in isolation. As such, this complex circuitry interfaces with pathways that mediate cognitive function and motor planning (Fig. 1.6). Within each of the cortical–BG structures, there are regions of convergence linking up areas that are associated with different functional domains. Convergence between terminals derived from different cortical areas in the striatum and STN permits cortical information to be disseminated across multiple functional regions. In addition, there are several interconnections in the system that contain reciprocal–nonreciprocal networks. The two major ones are the striatonigrostriatal pathway and the corticothalamocortical network. In addition, the VP–VS–VP also has a nonreciprocal component. Through these networks, the reward circuit influences cognition and motor control through several different interactive routes allowing information about reward to be channeled through cognitive and motor control circuits to mediate the development of appropriate action plans.

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CHAPTER

2

Electrophysiological Correlates of Reward Processing in Dopamine Neurons

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Abstract

Studies have identified three novel properties of the dopamine reward-prediction error signal. First, the dopamine response reports initially and unselectively many salient, potentially rewarding events and subsequently processes more specifically the reward-prediction error. This two-component structure restricts the earlier claimed salience coding to the initial component and explains aversive activations by physical impact rather than punishment. Second, the dopamine prediction error signal reflects subjective reward value and, more stringently, formal economic utility. A dopamine utility prediction error signal would be particularly useful for economic choices that maximize utility. Third, the dopamine signal fits well into formal competitive decision models, whereby it codes the output variable (chosen value) suitable for updating or immediately influencing main input variables (object value and action value). With these properties, the dopamine utility prediction error signal bridges the gap between animal learning theory (prediction error) and economic decision theory (utility).

INTRODUCTION

Dopamine has several functions in the brain. The neurologist knows dopamine from the movement disorders in Parkinsonian patients, who lack dopamine; the psychiatrist knows dopamine from psychotics, who may suffer from excessive dopamine processes; the cognitive psychopharmacologist knows dopamine from the many deficits caused by underfunctioning or overstimulated dopamine receptors in humans and animals; and the neurophysiologist knows dopamine from the reward responses of dopamine neurons. There seems to be no such thing with dopamine as "one neurotransmitter—one function." Research advances relate these diversities to different time courses of dopamine function, from tonic via slow to rapid, and to the various brain structures innervated by dopamine neurons [1].

This chapter will consider the most rapid dopamine function, which concerns primarily the signaling of reward in relation to its prediction. This signal is very similar in latency, duration, and sensitivity across dopamine neurons and contrasts with the widely diverse neuronal categories in other brain structures. I will describe advances in characterizing the dopamine reward-prediction error signal using behavioral tools of experimental economics, which are based on the well-developed concepts of economic choice theory. I will then formulate some hypotheses about the way this dopamine signal might function to update economic decision variables and to directly influence economic decisions. More details are found in a review from which this text is distilled [2].

BASICS OF DOPAMINE REWARD-PREDICTION ERROR CODING

Reward-Prediction Error

One of the simplest forms of learning involves error and error correction. Beyond the basic notion of incorrect behavior, "error" refers to the difference between an outcome and a prediction. In reinforcement learning, prediction errors drive learning according to the equation

$$V(t+1) = V(t) + \alpha \times PE(t) \tag{2.1}$$

with

$$PE(t) = \lambda(t) - V(t) \tag{2.2}$$

where PE is the prediction error, V indicates reward prediction, α the learning coefficient, t the trial, and λ the

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reward. A reward that is better than predicted will increase the associative strength, or prediction, carried by a stimulus; a reward that is worse than predicted with reduce the associative strength, or prediction; and a reward that occurs exactly as predicted will generate no change in associative strength or prediction [3]. The term of associative strength in animal learning theory can be translated into the notion of value in machine learning and economic decision theory. Thus, a stimulus acquires motivational value through prediction-error learning; it becomes a higher order reinforcer that itself can induce learning. The suitability of conditioned stimuli, along with unconditioned rewards, for learning is captured in temporal difference (TD) learning [4] by the equation

$$V(t+1) = V(t) + \alpha \times TDPE(t) \tag{2.3}$$

with

$$TDPE(t) = \left[\lambda(t) + \gamma \sum V(t)\right] - V(t-1) \tag{2.4}$$

where γ indicates the value decay associated with later rewards (temporal discounting) and t the time step during a trial. Actions do not have value themselves but can lead to the acquisition of valuable objects for the animal, which motivates the shorthand term of action value.

The majority of dopamine neurons (60–95%) in the pars compacta of the substantia nigra (SNc) and in the ventral tegmental area (VTA) report reward-prediction errors in humans, monkeys, rats, and mice (Fig. 2.1A); the remaining dopamine neurons fail to respond at all [5–10]. With food or liquid rewards that are better than predicted, or completely unpredicted, the response consists of a short, phasic increase in activity at latencies of <100 ms and durations of <200 ms ("activation"). With rewards that are worse than predicted, or completely omitted, the response consists of a depression of activity with similar latencies but somewhat longer durations. Rewards that occur exactly as predicted draw no dopamine response. Thus, the response reflects fully the bidirectional nature of prediction errors as conceptualized in Rescorla–Wagner learning [11,12]. Importantly, the response is sensitive to the temporal occurrence of reward and thus reflects a prediction error in time [13]. The reward response fulfills two formal prediction error tests. In blocking, a stimulus is not learned when the reward is fully predicted by another stimulus, and the dopamine response reflects the absence of prediction by the unlearned stimulus at the time of reward [14]. In conditioned inhibition, a stimulus explicitly predicts reward absence, and a reward occurring after that stimulus elicits an exaggerated positive-prediction error and correspondingly strong dopamine activation [15].

Unpredicted reward-predicting stimuli induce phasic activations in most dopamine neurons (Fig. 2.1A) [6,16] and induce striatal dopamine release [17]. These responses appear to concur with prediction V of the Rescorla–Wagner models but, on closer inspection, depend on the prediction of the reward-predicting stimuli and thus reflect higher order reward-prediction errors that are compatible with TD models (Fig. 2.1B and C) [5,7,18–20].

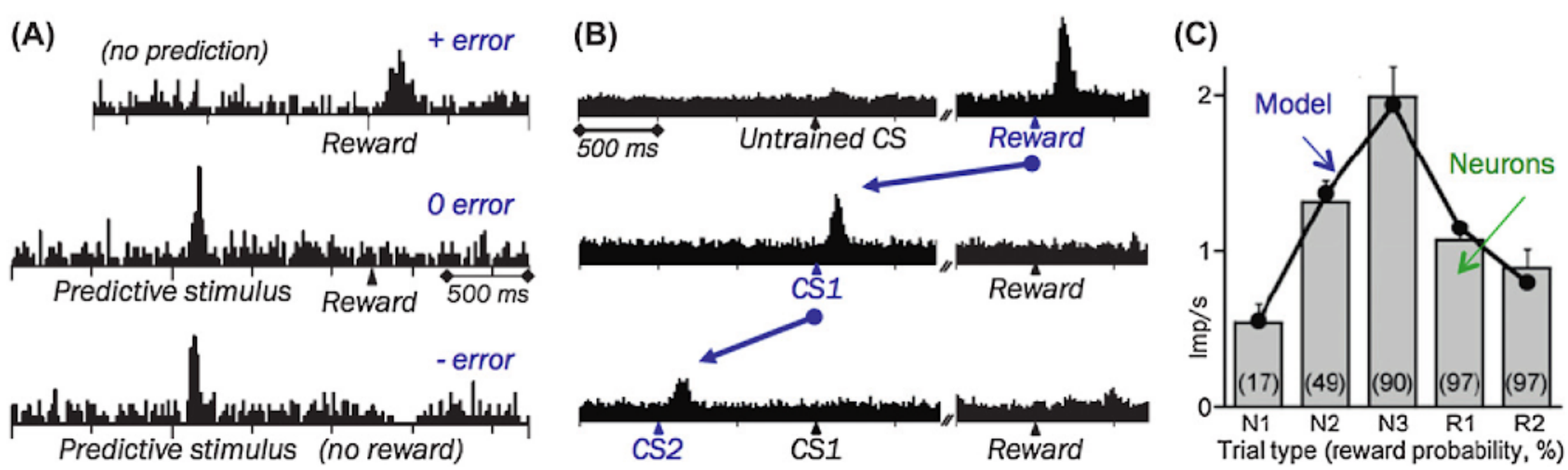

FIGURE 2.1 Dopamine reward-prediction error responses in monkeys. (A) Reward-prediction error responses at time of reward (right) and reward-predicting visual stimuli (left in bottom two graphs). The dopamine neuron is activated by the unpredicted reward, eliciting a positive reward-prediction error (blue +error, top); shows no response to the fully predicted reward, eliciting no prediction error (0 error, middle); and is depressed by the omission of predicted reward, eliciting a negative prediction error (−error, bottom). *(From Schultz W, Dayan P, Montague RR. A neural substrate of prediction and reward. Science 1997;275:1593–9.)* (B) Propagation of dopamine response from reward to first reward-predicting stimulus. CS2 and CS1, reward-predicting stimuli in delayed response task. *(From Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol 1998;80:1–27.)* (C) Reward-prediction error responses in serial reward task matching formal temporal difference prediction errors (averaged from 26 dopamine neurons). *Gray bars* indicate dopamine response amplitude at different sequence steps, *numbers* indicate reward probabilities in percentage. *Black line* shows time course of modeled prediction errors. *(From Enomoto K, Matsumoto N, Nakai S, Satoh T, Sato TK, Ueda Y, et al. Dopamine neurons learn to encode the long-term value of multiple future rewards. Proc Natl Acad Sci USA 2011;108:15462–7.)*

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Human neuroimaging studies report blood oxygen level-dependent neuromagnetic (fMRI) signals reflecting reward-prediction errors in the ventral midbrain [21]. Reward-prediction error signals are usually stronger in the ventral striatum [22,23], where they presumably reflect dopamine inputs to the area [24].

Response Components

The dopamine reward prediction error response develops over 50–200 ms from an initial, brief, and unselective activation component that detects any noticeable event, including "neutral" stimuli, conditioned inhibitors, and punishers [25–31]. Other cognitive and reward neurons show similar gradual developments from initial unselective reports to subsequent specific stimulus identification and discrimination [32,33], although inferotemporal feature detectors capture stimulus specificity immediately [34]. The components of dopamine responses are often not discriminable with easily identifiable stimuli but become distinctive with more demanding stimuli [19]. The unselective response part is boosted by physical stimulus intensity [29–31], similarity to rewarded stimuli (generalization) [26], rewarded context [35], and novelty [25]. These factors reflect physical salience, positive motivational salience, and novelty salience, respectively. In this way, dopamine neurons detect a wide spectrum of stimuli unselectively and thus are unlikely to miss major rewards. The short latency of the initial response component allows subjects to prepare actions very early, and the different forms of salience are likely to sharpen neuronal processing in the subsequent reward component. As the main dopamine response component recognizes the absent or negative reward value of neutral stimuli and punishers, the neurons process the value of all stimuli accurately after the initial unselective response and thus will not mislead the animal.

The initial lack of selectivity of the dopamine response may explain why responses to unrewarded stimuli and punishers were interpreted as salience and aversive signals. Testing neutral stimuli without assessing reward-prediction error reveals only the unselective response, which could give rise to the interpretation of a prime salience function of dopamine responses [27], whereas salience concerns only the initial response. Testing punishers without controlling for physical impact, reward generalization, and reward context may encourage interpretations toward aversive activations and general motivational salience processing [36,37], whereas adequate controls reveal that the activations to punishers reflect their physical impact rather than their aversiveness [29]. Thus, recognition of the gradual development of the two-component dopamine response may help to identify its true character.

Reward Learning

Reflecting reward-prediction errors, dopamine responses should follow the development of reward predictions during learning. The changes should become apparent when reward delivery elicits prediction errors. While learning cognitive tasks via intermediate, more simple subtasks, dopamine neurons show repeatedly transient responses to rewards in each subtask when predictions are not yet fully established; these responses disappear after acquisition in every subtask (Fig. 2.2A and B) [5]. With the disappearing reward responses, responses to reward-predicting stimuli appear gradually during learning [5,14] and then disappear again with extinction [28]. Voltammetrically measured dopamine concentrations in the rat ventral striatum show comparable reductions in reward responses and increases in stimulus responses during learning [17]. Thus, dopamine responses develop systematically in parallel with reward-prediction errors during learning.

Comparisons with the Rescorla–Wagner and TD learning rules suggest that the bidirectional dopamine reward-prediction error response would be an ideal teaching signal for learning and updating of decision variables. Indeed, electrical and optogenetic stimulation of dopamine neurons induces operant learning of lever pressing and nose poking in rodents [38–41]. The learning function may involve, in its most simple way, the action of dopamine release on postsynaptic neurons. In a hypothetical, anatomically based model [5], the signal from SNc and VTA dopamine neurons would impact on postsynaptic neurons in dorsal and ventral striatum (caudate nucleus, putamen, nucleus accumbens), frontal cortex, and amygdala through diverging, widespread projections (Fig. 2.2C and D). Dopamine release would affect neuronal transmission at a triad arrangement composed of dendritic spines, presynaptic afferents, and dopamine inputs [42], such that the dopamine signal enhances synaptic transmission from recently active inputs while leaving inactive synapses unchanged. Experimental evidence demonstrates dopamine-dependent plasticity at striatal neurons carrying D1 dopamine receptors [43,44]. In correspondence to these dopamine effects on behavioral learning and neuronal plasticity, lesion and psychopharmacologic studies suggest the necessary role of dopamine impulse responses and neurotransmission in simple forms of associative learning [45,46]. Thus, the dopamine reward-prediction error signal may exert a behavioral function on basic forms of reward learning.

In addition to reward learning [38–41], stimulation of dopamine neurons elicits also immediate behavioral reactions [40], suggesting that dopamine activation induces motivational value (and satisfaction if we accept emotional terms). This activation mimics the neuronal

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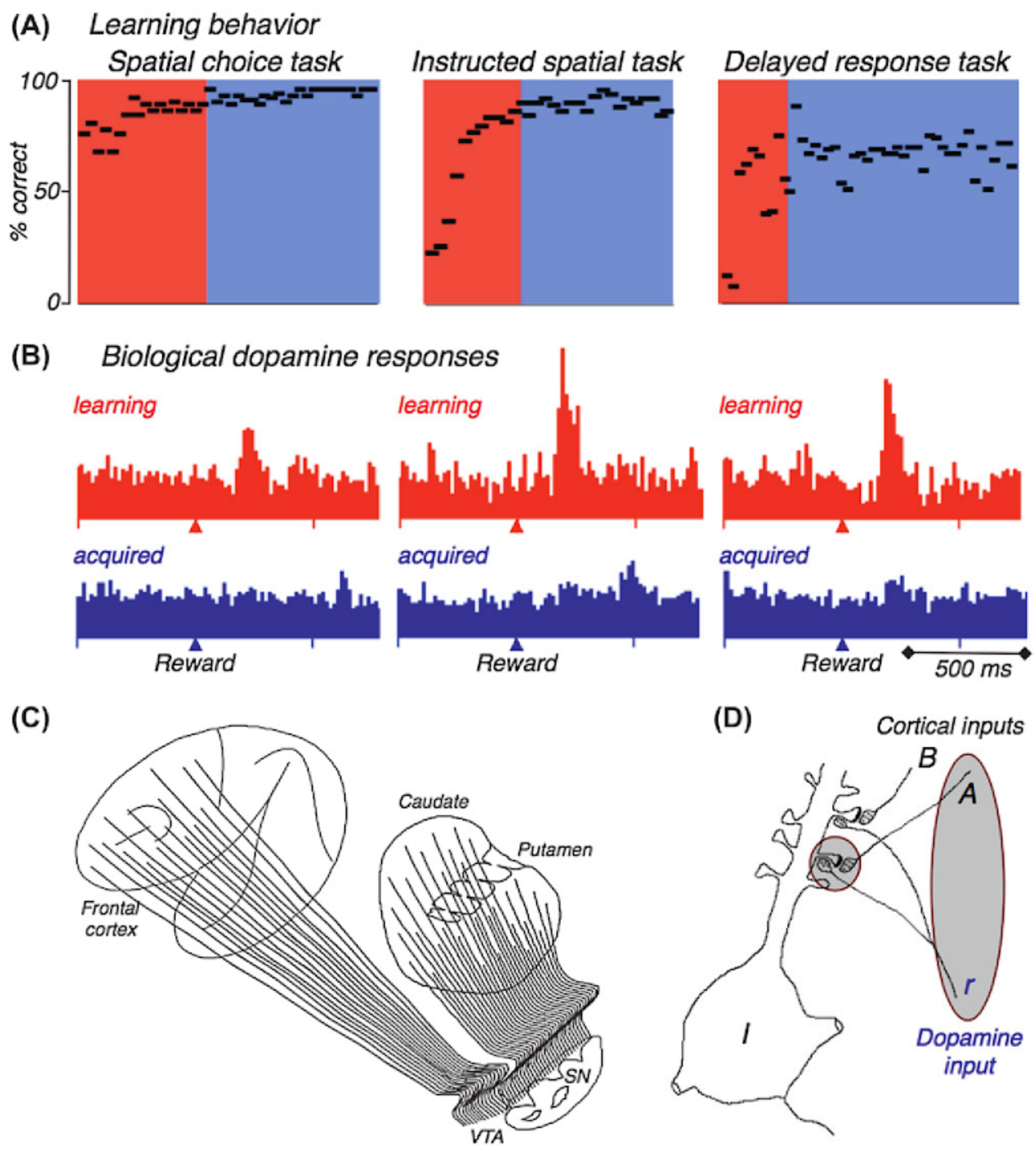

FIGURE 2.2 Dopamine responses and their hypothetical influences during learning. (A) Stepwise learning of spatial delayed-response task via intermediate spatial subtasks. Each dot shows mean percentage of correct behavioral performance in 20–30 trials during learning (red) and asymptotic performance (blue). (B) Positive dopamine reward-prediction error responses during learning of each subtask, and their disappearance during acquired performance. Each histogram shows averaged responses from 10–35 monkey dopamine neurons during the subtasks shown in (A). *((A) and (B) are from Schultz W, Apicella P, Ljungberg T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J Neurosci 1993;13:900–13.)* (C) Global dopamine reward signal advancing to striatum and cortex. The population response of dopamine neurons in substantia nigra (SN) pars compacta and ventral tegmental area (VTA) can be schematized as synchronous, parallel activity advancing from the midbrain to the striatum (caudate and putamen) and cortex. *(From Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol 1998;80:1–27.)* (D) Differential influence of dopamine signal on selectively active corticostriatal transmission. The dopamine reinforcement signal (r) modifies conjointly active synapses (A) at the striatal neuron (I) but leaves inactive synapses (B) unchanged. *Gray circle and ellipse* indicate simultaneously active elements. *(From Smith AD, Bolam JP. The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. Trends Neurosci 1990;13:259–65; Schultz W. Potential vulnerabilities of neuronal reward, risk, and decision mechanisms to addictive drugs. Neuron 2011;69:603–17.)*

activation evoked by a positive reward-prediction error (Figs. 2.1A,B, 2.2B, and 2.3D,F). It is reasonable to assume that a natural dopamine activation induced by positive reward-prediction errors might have similar effects on behavior. The effects may be more biasing or modulatory, as a real reward induces also nondopamine responses that may mitigate the dopamine effects. Nevertheless, only positive reward-prediction errors induce dopamine activations and thus biasing effects on behavior, whereas simple reward occurrence without positive-prediction error does not stimulate dopamine neurons. Thus, the biasing effects of dopamine neurons occur only when a reward is better than predicted. However, the positive reward-prediction error increases at the same time as the reward prediction, in correspondence with Rescorla–Wagner and TD learning [3,4]. The next

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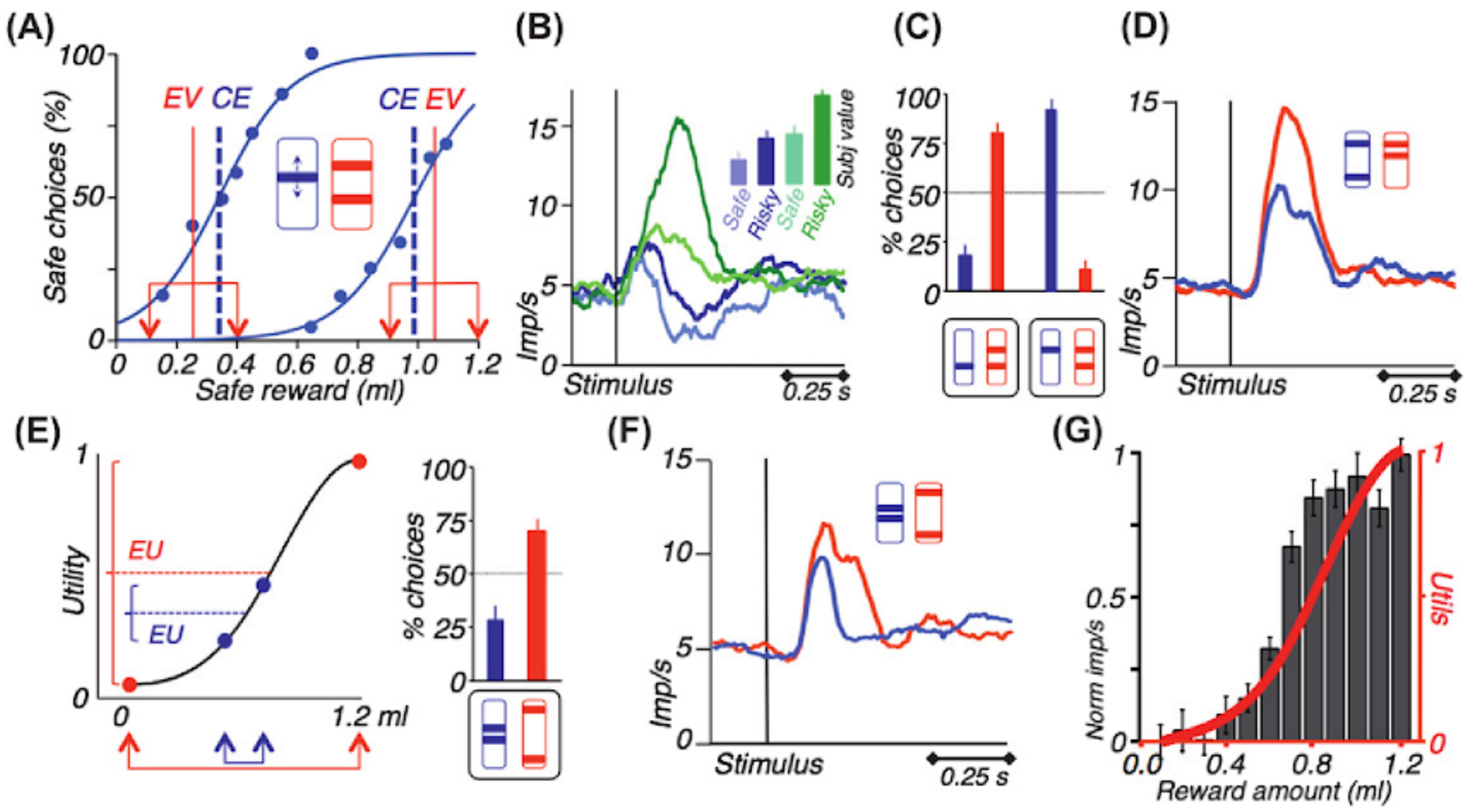

FIGURE 2.3 Risk and utility coding in monkey dopamine neurons. (A) Psychophysical assessment of risk attitude in oculomotor choices. The certainty equivalent (CE) indicates the subjective value of the risky gamble as the magnitude of the adjustable safe outcome (blue) at choice indifference against the gamble with the same expected value (EV, red). A CE > EV indicates risk seeking (left), a CE < EV indicates risk avoidance (right). *Red arrows* indicate the two outcomes of each gamble. *Insets* show choice set with adjustable safe outcome (blue) and fixed gamble (red). The *higher bar* indicates higher reward amount, *two bars* indicate a binary equiprobable gamble ($p = .5$ for each outcome). *(From Stauffer WR, Lak A, Schultz W. Dopamine reward prediction error responses reflect marginal utility. Curr Biol 2014;24:2491–500.)* (B) Risk increases subjective value responses of dopamine neurons. The subjective value for safe black currant juice (green) is higher than for safe orange juice (blue) and higher for binary gambles than safe outcome of the two juices (risk seeking), as assessed psychophysically by choice indifference against a common reference reward *(inset)*. Amounts are 0.45 mL for safe juices and 0.3 and 0.6 mL for the two gamble outcomes. Dopamine neurons show analogously ranked neuronal responses to the reward-predicting stimuli. *(From Lak A, Stauffer WR, Schultz W. Dopamine prediction error responses integrate subjective value from different reward dimensions. Proc Natl Acad Sci USA 2014;111:2343–8.)* (C) Choices between safe and risky outcomes. Monkeys avoid the low certain reward (*single blue bar, bottom*), which is equal to the low gamble outcome (*double red bars, left*) and prefer the high safe reward (equal to high gamble outcome) (right) in choices against an equiprobable gamble. These choices satisfy first-order stochastic dominance, indicating rational preferences. (D) Dopamine responses to upper gamble outcomes (positive-prediction error) satisfy first-order stochastic dominance (averages from 52 neurons). The red gamble dominates the blue gamble, as the *top bars* indicate equal reward amounts and the *lower bar* is higher for the red compared to the blue gamble. (E) Risk-seeking behavior in gambles with mean-preserving spread. Left: Plotting gamble values onto the individually assessed utility function demonstrates higher expected utility (EU) for the more widely spread gamble (red, compared to blue). Right: In the tested range, monkeys prefer equal-chance gambles with higher mean-preserving spread (red over blue gamble), thus satisfying second-order stochastic dominance for risk seeking and indicating meaningful incorporation of risk into choices. (F) Dopamine responses to upper gamble outcomes satisfy second-order stochastic dominance (averages from 52 neurons). (G) Utility-prediction error signal in dopamine neurons. *Red*, Utility function; *Black*, Corresponding, nonlinear increase in population response to unpredicted juice rewards (positive-prediction error; $n = 14$ dopamine neurons). *((C)–(G) are from Stauffer WR, Lak A, Schultz W. Dopamine reward prediction error responses reflect marginal utility. Curr Biol 2014; 24:2491–500.)*

time the same reward occurs, the prediction has already increased, and the reward elicits only a lower or no positive-prediction error and dopamine activation, and the behavioral stimulating effect is lower. Only a higher reward will now have the same influence on behavior. To bring down the prediction again requires a negative reward-prediction error from a smaller reward evoking a dopamine depression, but smaller-than-predicted rewards are typically avoided. In this way, for rewards to have similarly motivating influences on behavior via the dopamine signal, they need to become higher and higher. This circle of stimulating behavior and at the same time increasing the prediction may explain why we strive for ever higher rewards. If we argue in terms of satisfaction that is induced by dopamine activation, only higher-than-expected rewards produce satisfaction, whereas the same old rewards leave us unimpressed. But as higher rewards induce higher predictions, to obtain the same satisfaction from a positive-prediction error-signaling dopamine response will require continuously increasing rewards.

SUBJECTIVE VALUE AND FORMAL ECONOMIC UTILITY CODING

Subjective Value

The function of rewards reflects biological needs for nutritional and other substances. The value of rewards

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depends on the organism's momentary requirements and attitudes and thus is subjective. Subjective value cannot be derived directly from physical or sensory properties of rewards but requires behavioral measures. Particularly useful methods involve choices between different rewards and their psychophysical assessment against a common reference reward. Subjective value estimated in these ways can be expressed in physical units of the reference reward at points of equal preference (indifference points, measured in milliliters of juice, numbers of pellets, pounds, euros, or dollars). The reference reward defines a common currency, which is called a numeraire in economics; all other rewards can be quantitatively stated in real-number multiples of the numeraire.

Although subjective value can be measured in external, physical units, we do not know how much a milliliter of juice or a pound is worth to the individual decision-maker; we do not know how these physical units are scaled internally. All we know is that the internal value usually relates in a positive monotonic fashion to the externally scaled subjective reward value, as long as satiation is avoided. Higher externally scaled subjective value means higher internal value. However, this relationship is not necessarily proportional along the whole value range; thus it provides only rank-ordered, ordinal internal measures. We will see below how to obtain internal value measures on a continuous, numeric, cardinal scale by estimating utility with specific choice protocols.

Subjective Value Derived From Risk

One of the major determinants of subjective value is risk, which reflects the general notion that all environmental events, including rewards, are inherently uncertain. The simplest and most controlled form of risk can be tested with binary, equiprobable gambles ($p = .5$ for each outcome), in which a large and a small reward occur with equal chance. Here risk is defined entirely by the statistical variance and can be varied by changing the outcomes by equal amounts in opposite directions without changing the statistical expected value (EV; "mean-preserving spread") [47]; another form of risk, skewness risk, is absent, and subjective probability distortion [48] is minimal and symmetric. The influence of risk on subjective value is conveyed by the notions of risk avoidance and seeking, which indicate reduced or enhanced preferences, and thus subjective value, for risky compared to safe rewards of the same average magnitude.

Risk attitudes are conveniently assessed by the certainty equivalent (CE) in psychophysical choices against an adjustable safe reward; the physical amount of safe reward at choice indifference indicates the subjective value of the gamble. In low reward ranges, rhesus monkeys show CEs higher than EVs, indicating risk seeking, whereas in higher ranges, CEs are lower than EVs, indicating risk avoidance (Fig. 2.3A) [49]. The employed test stimuli contain bars whose vertical height indicates reward amount; two bars predict an equal chance of obtaining the upper or lower juice amount (Fig. 2.3A, inset). Dopamine neurons show stronger responses to more preferred liquid reward of the same amount (eg, black currant over orange juice) and, corresponding to the enhancing influence of risk on subjective value in the low reward range, the responses are increased with risky rewards of identical EV (Fig. 2.3B) [50]. Corresponding to the electrophysiological responses, voltammetrically assessed dopamine release to risky cues in the ventral striatum is reduced in risk-avoiding rats and enhanced in risk seekers [51]. Monkeys' choices of risky rewards are meaningful by satisfying first-order stochastic dominance; a binary gamble whose lower outcome equals that of a safe reward is preferred over that reward, because the subject may win and cannot lose anything by choosing the gamble; by contrast, a gamble whose upper outcome is equal to a safe reward is dispreferred over that reward because the subject may get the low gamble outcome and thus lose compared to the safe reward (Fig. 2.3C) [49]. Dopamine neurons show correspondingly stronger responses to first-order stochastically dominating gambles (Fig. 2.3D). Thus, in this and other experiments, monkeys are risk seekers in small reward ranges, risk affects subjective reward value in a corresponding manner, and dopamine neurons reflect the influence of risk on value and thus code subjective, rather than objective, reward value.

Utility

Whereas subjective value estimated from choices follows an objective, physical scale (eg, milliliters of juice at choice indifference), formal economic utility goes one step further and reflects a private, internal measure of subjective value [52] (often called utils). Utility is a mathematical representation of the preference structure of the individual decision-maker that can be described by a continuous function of physical value, such as u(x) [53]. Neuronal response functions vary in a near-continuous way and have cardinal properties; they are valid irrespective of offset and gain (positive affine transformation). Therefore, the represented utility should also be continuous, quantitative, numeric, and cardinal. Such properties can be achieved in choices involving gambles with known probabilities [54], such as the binary gambles already described. The iterative, chaining procedure provides a convenient method for estimating cardinal utility from such gambles [55,56]. The utility functions estimated in monkeys are convex

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in low reward ranges and concave at higher ranges (Fig. 2.3E) [49], replicating the pattern of risk seeking and risk avoidance seen in the direct risk tests (Fig. 2.3A). When calculations on the utility function suggest that a mean-preserving riskier gamble has higher expected utility than a less risky gamble, which indicates risk seeking, monkeys show corresponding preferences for the riskier gamble (Fig. 2.3E); these choices satisfy second-order stochastic dominance for risk seeking [49,57], indicating meaningful reflection of risk in the utility function. Dopamine responses show correspondingly higher responses to the riskier gamble (Fig. 2.3F) [49] and thus follow second-order stochastic dominance, suggesting adequate incorporation of risk into neuronal utility.

The systematic variation in risk attitude and the behavioral and neuronal satisfaction of first- and second-order stochastic dominance suggest that the behavioral tools for assessing utility are adequate for monkeys. Already the simplest reward test suggests that dopamine neurons code utility; delivery of free, unpredicted reward juice, which constitutes a positive reward-prediction error, induces a nonlinear increase in dopamine responses that follows the behavioral utility function (Fig. 2.3G) [49]. Economic theory requires gambles with known probabilities for estimating numeric utility; testing with gambles satisfying this requirement, such as the binary gambles described above, results in very similar nonlinear changes in dopamine responses [49]. With gambles of identical variance, the dopamine prediction error response to the upper gamble outcome is small in lower reward ranges in which the utility slope is flat, larger in higher reward ranges with steeper utility slope, and smaller again at highest reward ranges with flatter utility slope. Thus, the dopamine response reflects a prediction error in utility. These nonmonotonic responses reflect, but do not necessarily code, the nonmonotonic marginal utility (first derivative of utility) that underlies the inflected utility function. Although neuronal coding is indistinguishable between marginal utility and utility prediction error with these equal-risk gambles, the dopamine responses to free reward increase with reward amount rather than marginal utility, which identifies coding of utility prediction error rather than marginal utility. The two terms relate well to each other, as marginal utility and prediction error conceptualize deviations from a reference (current wealth and prediction, respectively), but dopamine neurons distinguish between the two by coding utility prediction error and not marginal utility.

Taken together, three lines of argument suggest that dopamine neurons meaningfully incorporate risk into subjective value and utility coding. Dopamine reward-prediction error responses increase when risk enhances subjective value (Fig. 2.3B), they follow second-order stochastic dominance (Fig. 2.3F), and they increase nonlinearly with free reward (Fig. 2.3G) and gambles in close correspondence to formal economic utility [49]. In coding utility, dopamine neurons process reward information in the most formal and constrained way defined by economic choice theory.

DOPAMINE AND DECISION-MAKING

Updating of Decision Variables

A popular minimal generic model of decision-making [58,59] involves the competition between two options. The hypothetical model involves forward excitation of independent input activity, mutual lateral inhibition, and a threshold mechanism, such that only the stronger input leads to an output, whereas the weaker input is lost (Fig. 2.4). This winner-take-all (WTA) mechanism turns the graded difference between the inputs into an all-or-none output that reflects only the value of the stronger option. The basic input variables to this model are object value, action value, and their derivatives and combinations. Object value denotes the value of a stimulus or reward object and is appropriate for decisions about goods, as conceptualized in economics. Action value indicates the value obtained by an action and is appropriate for decisions about actions, as modeled in machine learning. To constitute a neuronal decision mechanism, separate pools of neurons would code the value of each input object or action separately and irrespective of the behavioral choice. Neurons coding object value or action value are found in the orbitofrontal cortex [60] and striatum [61], respectively; these structures receive dense inputs from dopamine neurons.

The reward-prediction error reflected in dopamine neurons results from the subtraction of predicted reward value from experienced value. The experienced value is the received reward for Rescorla–Wagner models (Eq. (2.2)) and may include higher order rewarded stimuli for TD models (Eq. (2.4)). The experienced value reflects the outcome of the decision process and is called the chosen value. Chosen value reflects the value of the option that won the competitive decision process; it is the result of the decision rather than being its input and thus is usually considered to be a postdecision variable. The predicted reward value is the current object value or action value of the chosen option. Predicted values derive exclusively from recent outcomes in model-free reinforcement processes but may incorporate predictions from model-based reinforcement learning. Although being particularly suitable for model-free learning, the dopamine signal incorporates predictions from models of the world, as shown with different probability distributions, sequential

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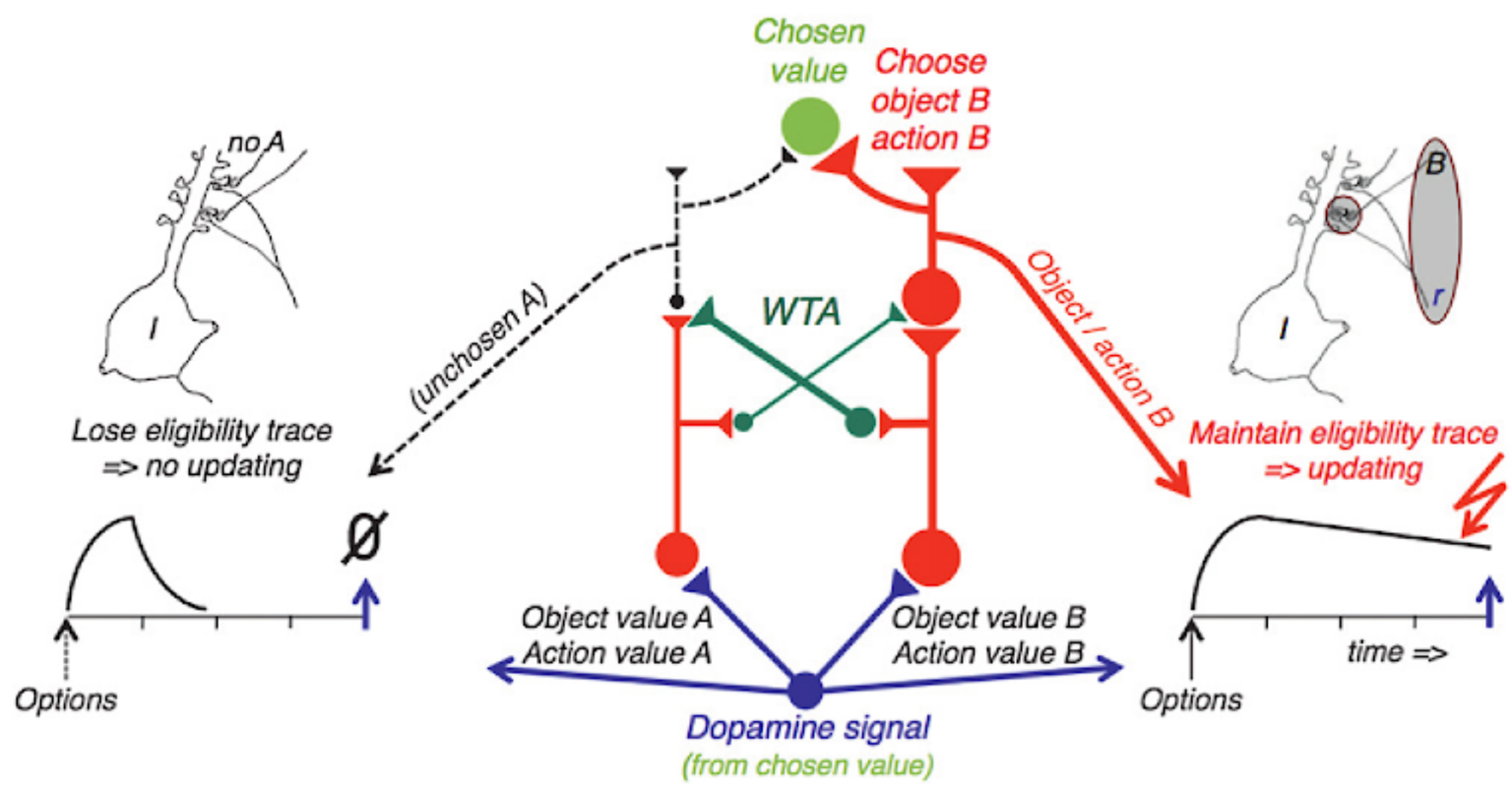

FIGURE 2.4 Hypothetical model for updating of decision variables by the dopamine signal. In a competitive decision process, the global dopamine reward-prediction error signal acts on postsynaptic neurons via eligibility traces. Eligibility traces are selectively stabilized by neurons coding the chosen object or chosen action (right) but decay for neurons coding the unchosen option (left). Thus, the dopamine signal updates only object values or action values of options that were chosen. The dopamine prediction error derives from chosen value (experienced minus predicted object value or action value of chosen option). *Gray zones at top right* indicate common activations. The weight of *dots* and *lines* indicates levels of neuronal activity. *Dotted lines* indicate inputs from unchanged neuronal activities. *Crossed green connections* are inhibitory; *WTA*, winner-take-all mechanism. The weights of dots and lines in the circuit model indicate level of neuronal activity. *I*, striatal neuron; *r*, dopamine reinforcement signal. Scheme developed together with Fabian Grabenhorst. *Modified from Schultz W. Neuronal reward and decision signals: from theories to data. Physiol Rev 2015;95:853–951.*

movements, and reversal sets [15,62,63]. A prediction error suitable for updating object value and action value would result from the subtraction of object value or action value of the chosen option from the experienced chosen value. This term constitutes a reward prediction error in chosen value. Indeed, dopamine neurons and voltammetric striatal dopamine release code such a chosen value prediction error during choices [51,64]. Although we use the generic term of value, the best-defined and adequate metric for value that should be coded in all these signals is economic utility. The dopamine signal codes formal economic utility [49] and integrates reward delay, reward risk, and various liquid and food rewards [50,65].

With these characteristics, the dopamine prediction error signal is suitable for updating the input variables to the competitive decision process for the next trial, namely object value and action value, following (Eqs. (2.1)–(2.4)). The hypothetical updating model shown in Fig. 2.4 represents a possible mechanism. Despite the indiscriminate propagation of the dopamine signal to postsynaptic neurons (Fig. 2.2C), specificity in updating may result from the eligibility traces that make previously active neurons and synapses selectively sensitive to the reinforcing effects of the reward resulting from the chosen option [4]. Eligibility traces may decay rapidly unless they are stabilized by neuronal activity associated with the chosen object or action. In this way, the chosen value signal of dopamine neurons would selectively affect only object values or action values in neurons that contributed to the decision, as marked by maintained eligibility traces but leave the values of the unchosen option unchanged. For example, choice of object B would lead to a dopamine reward-prediction error signal derived from the chosen value minus object value B that would serve to selectively update object value B. The selectivity in updating is due to the eligibility trace from object B being maintained by activity from the chosen object B, whereas the eligibility trace from object A decays before the reinforcement signal can act on it. The dopamine updating influence would involve known synaptic plasticity [43,44]. Taken together, the updating of decision variables by the dopamine prediction error signal in chosen value can be conceptualized on the basis of a simple, biologically plausible WTA decision mechanism.

Direct Dopamine Influences on Choices

In addition to learning and updating, electrical or optogenetic stimulation of dopamine neurons or striatal neurons carrying specific dopamine receptors induces immediate behavioral actions and differential choice biases [40,66]. These effects may involve direct dopamine actions on striatal synapses [67]. Correspondingly, reduction of D1 receptor stimulation impairs spatial working memory and memory-related neuronal activity in monkey frontal cortex [68,69]; reduced dopamine bursting activity in mice with knocked out NMDA receptors on dopamine neurons is associated with

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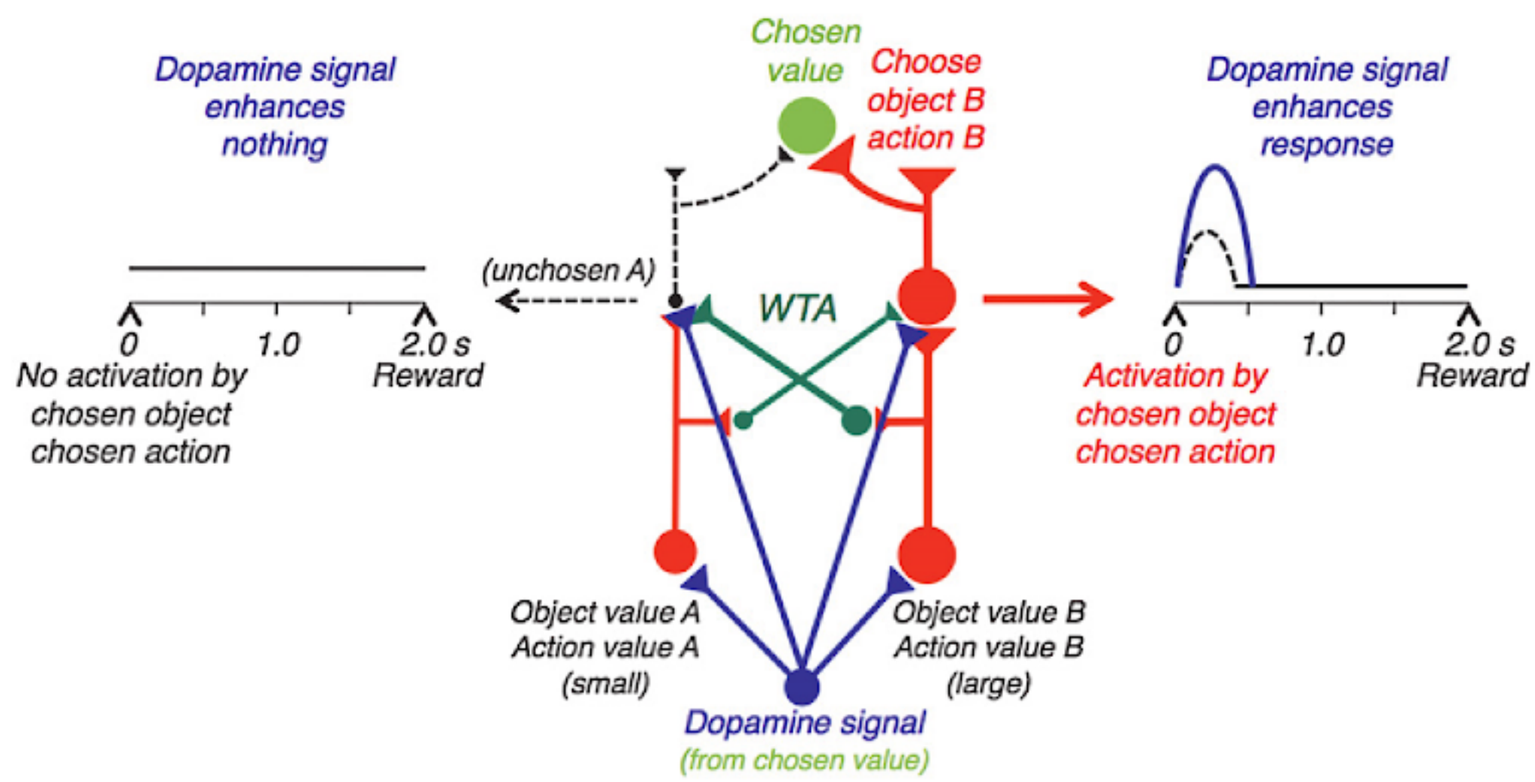

FIGURE 2.5 Hypothetical model for immediate influence of the dopamine signal on neuronal decision mechanisms. The dopamine prediction error signal of chosen value may have two distinguishable influences. First, it may boost differences between neuronal signals coding object value or action value at the input to the competitive decision mechanism (bottom). Second, it may enhance activities selected by the winner-take-all (WTA) mechanism that represent chosen object or chosen action (top right), without affecting activity that was lost in the WTA competition (top left). *Modified from Schultz W. Neuronal reward and decision signals: from theories to data. Physiol Rev 2015;95:853–951.*

prolonged reaction times [45]. Thus, dopamine signals may have immediate effects on decision-making, distinct from their reinforcement function.

The hypothetical competitive decision model may be modified to capture these immediate dopamine effects (Fig. 2.5). The dopamine prediction error signal derived from chosen value may exaggerate differences in neuronal activity in two possible ways. First, the signal may affect object value or action value signals at the input of the decision process. Local optogenetic stimulation of striatal neurons carrying specific dopamine receptors affects action values for contralateral actions [66]. Although this experimental effect may rely on locally specific dopamine influences, which may not exist in natural choices, it may also function by enhancing the frequently occurring differences in postsynaptic value signals in many behavioral tasks [66]. Second, the dopamine signal may boost exclusively neuronal activity reflecting the chosen object or chosen action that survived the WTA competition, without affecting signals that were lost by the WTA mechanism (Fig. 2.5, right); only the neuronal signal for the chosen option, and not for the unchosen option, would benefit from the immediate effects of the dopamine prediction error signal, thus sharpening the WTA selection. Taken together, the immediate influence of the dopamine prediction error signal on behavioral choices can be captured by a simple WTA decision mechanism. The possible implementation of this hypothesis needs to be worked out by considering the particular neuronal activities and circuits in the postsynaptic structures such as striatum, frontal cortex, and amygdala.

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CHAPTER

3

Appetitive and Aversive Systems in the Amygdala

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Abstract

The amygdala has been traditionally considered to process information about aversive stimuli, but it is now recognized to mediate emotional behaviors elicited by stimuli of both valences. Electrophysiological studies have shown that the amygdala contains distinct appetitive and aversive networks of neurons. The development of new molecular tools for interrogating neural circuit function has rapidly advanced our understanding of these networks. Selective activation of appetitive or aversive amygdalar networks can elicit innate valence-specific autonomic responses, and can induce Pavlovian and operant learning. An important goal for scientific inquiry is to understand the functional role of the bidirectional interactions between appetitive and aversive systems in the amygdala and networks in the cerebral cortex that implement cognitive functions; the pathophysiology of psychiatric disorders probably involves dysfunctional interactions between these cognitive and emotional systems. Studies have begun to describe how activity in appetitive and aversive systems is updated by cognitive operations, and how such activity may also influence cognitive functions like attention.

INTRODUCTION

Anticipatory emotional responses to sensory stimuli require an agent to predict accurately the positive or negative emotional outcome associated with a stimulus presentation. This prediction relies on more than knowing the link between a sensory stimulus and a reinforcement, because such associations may differ depending upon the circumstances, as may the emotional meaning of the associations. For example, a particular stimulus, such as an unopened bottle of Romanée–Conti, may elicit a positive anticipatory emotional feeling only when it appears in circumstances in which opening the bottle is a possibility. Even then, its appearance may produce a positive emotional response only if one is not tired of drinking wine from this vineyard. The link between a sensory stimulus and an emotional response thereby relies on knowing how a stimulus, potential actions, and current circumstances—or context—together predict a particular outcome. Of note, context here is defined broadly as the set of circumstances in which the subject operates, including internal (abstract cognitive and homeostatic) and external (social and environmental) states [1–3]. As a result, a neural representation of the emotional significance of a stimulus must take into account contextual information, which includes information about internal and external variables as well as operant contingencies.

A neural representation of emotional significance bears similarity to neural representations posited to play a critical role in economic decision-making. In economic decision-making, a neural representation of stimulus value for two or more stimulus options must be computed online, taking into account context-dependent stimulus–outcome relations as well as internal and external contextual information that can adjust the value of a particular reinforcement outcome at a given moment [4–7]. Moreover, the values of stimuli, the values of actions, and "state value"—the value of the overall situation of an organism at a given moment—are essential variables in theoretical accounts of learning [8,9], and these theoretical accounts remain influential in understanding how previously neutral stimuli develop the capacity to generate emotional responses through such learning. Therefore, the acquisition of neural representations of the value of stimuli is also critical for economic decision-making. The coordination of anticipatory emotions, value-based decision-making, and reinforcement learning all probably share

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computational mechanisms that allow an agent to predict the relationship between sensory stimulus, actions, context, and meaningful outcomes.

Many of the brain areas that have been implicated in emotional processing—such as the amygdala—also are thought to play an important role in value-based decision-making [2,10–14]. Traditionally studied as a center essential for the acquisition and expression of defensive behaviors elicited by an aversive unconditioned stimulus (US) or by a conditioned stimulus (CS) paired with an aversive US (reviewed in [13]), the amygdala was confirmed by a 2014 meta-analysis to be an area of overlapping activity in value processing for both aversion and appetitive information in human functional imaging studies [15]. Substantial evidence indicates that the amygdala is involved in learning the relationship between a previously neutral CS and both appetitive or aversive reinforcement (US), as well as in coordinating responses to these stimuli [10,13,14,16–19].

The focus of this chapter is to review studies that have begun to describe in more detail the role of the amygdala in both appetitive and aversive processes in animal model systems. This work spans rodents and monkeys. Work in rodents has been particularly successful at characterizing detailed circuit-level mechanisms within the amygdala that mediate various forms of valence-specific emotional behavior. Studies in nonhuman primates have been particularly helpful for examining the relationship between the amygdala and cortical processing mediating various cognitive functions. Interactions between the amygdala and the prefrontal cortex is likely to be critical for updating or regulating valence-specific neuronal representations in the amygdala in a context-dependent manner. At the same time, neural representations of the emotional or motivational significance of stimuli in the amygdala are likely to influence cognitive functions, including processes such as decision-making and attention. Overall, the investigation of how amygdalar and cortical processing interact is likely to prove critical for understanding the pathophysiology of many psychiatric disorders.

Valence in the Amygdala

A long tradition of work has implicated the amygdala in processes related to emotional valence [10,13,14,16,20–25]. Classic studies linked the amygdala to the acquisition and expression of behavioral and physiological responses to aversive CSs [26,27]. It remained unclear, however, whether the same or different neurons participated in emotional learning and behavior for both positive and negative valences because prior studies typically did not examine the physiological response properties of neurons during both appetitive and aversive classical conditioning procedures.

Paton et al. [22] established that in fact the amygdala appears to contain separate appetitive and aversive neural systems. They applied a trace-conditioning task (a version of classical conditioning in which a brief temporal gap is inserted between the CS and the US). Novel, abstract visual CSs were followed by a US: a liquid reward, nothing, or an aversive air puff directed at a monkey's face. During conditioning, single-neuron activity in the amygdala was recorded. Neural signals related to sensory properties of the visual CSs themselves were disentangled from signals related to reinforcement contingencies by reversing the contingencies during each experiment. Individual amygdala neurons were often sensitive to this reversal: neurons would respond preferentially to either positively or negatively conditioned CSs both before and after the reversal. These neurons updated their response to a CS with a time course fast enough to account for behavioral learning of reversed reinforced contingencies.

Subsequent studies demonstrated that the neuronal populations encoding the valence of a CS provide a representation of the positive or negative overall value of the animal's state throughout the various events occurring during an entire trial (as opposed to being limited to the CS presentation) [28]. For example, the response to a fixation point, which monkeys voluntarily foveate to commence a trial, reflects the mildly positive value that this stimulus possesses for motivated subjects. Neurons belonging to the appetitive system tend to increase their firing rate in response to fixation-point appearance, but neurons of the aversive system tend to decrease their firing rate to the same stimulus. The responses to USs also reflected the valence-specific encoding properties of these neuronal populations. Other studies have reported neural signals in the amygdala that reflect expected reward value over long timescales during a task that involves planning [11], consistent with the encoding of state value across a series of planned actions.

The existence of cells encoding valence raises a fundamental question about the organization of circuits within the amygdala: do cells that respond preferentially to either rewarding or aversive events form distinct circuits? Reconstruction of the anatomical location of valence-encoding cells had failed to reveal clustering of neurons encoding a particular valence [22,28], suggesting that neurons within the appetitive and aversive systems in the amygdala were intermingled. Zhang et al. [29] applied a cross-correlogram (CCG) analysis to examine the functional connectivity between neurons simultaneously recorded during trace conditioning. Functional interactions between pairs of amygdala cells were related to their response properties, and these interactions also were observed to be task modulated [29].

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Peaks in CCGs at short latencies were significantly more likely to be observed if two neurons shared the same valence preference than if they did not. Thus valence-encoding neurons in the amygdala appear to form distinct circuits with other neurons encoding the same valence; these circuits could potentially guide relevant valence-specific behaviors, such as approach or avoidance [29]. However, because traditional methods for manipulating neural activity typically rely on anatomical clustering of neurons sharing physiological response properties in order to activate or inactivate neurons encoding a similar signal, the apparent lack of anatomical organization in the amygdala presented an experimental challenge both for understanding the causal role of neurons in mediating behavior and for understanding the circuit-level mechanisms that mediate valence-specific functions.

A link between neural activity in valence-specific circuits in the basolateral amygdala (BLA) and appropriate behavioral output has been established by exploiting new molecular techniques for identifying, marking, and manipulating neural activity based upon the response properties of targeted neurons. These approaches utilize activity-dependent and inducible systems to label only cells involved in valence-specific processes. For example, Gore et al. [24] used a lentivirus construct in which the expression of the immediate early gene c-fos, a molecular marker of neural activity, also drove the expression of channelrhodopsin (ChR2) linked to enhanced yellow fluorescent protein and a nuclear-localized mCherry [14,24]. The temporal expression pattern of this viral construct provided a two-time-point molecular marker of neuronal activity because c-fos is only transiently expressed after neural activity is elicited. During this early time window, expression of mCherry cannot be detected; by contrast, the detection of mCherry occurs with a longer latency after neural activity is elicited. As a result, c-fos marks neurons activated by a recent stimulus (e.g., 1 h earlier), and mCherry marks neuron activity in response to a stimulus that occurred further back in time (e.g., 18 h previous). Consistent with electrophysiological studies, using this approach Gore et al. [24] identified distinct, but anatomically intermingled, neuronal ensembles in the BLA that responded differentially to an innately appetitive US (nicotine, at a dose that elicited conditioned place preference) and an innately aversive US (footshock, which can be used to drive fear conditioning). Moreover, if the authors presented only a single stimulus to activate neurons, ChR2 could be expressed in either the appetitive or the aversive population of neurons selectively. Thus, despite the fact that neurons belonging to appetitive and aversive systems appear to be anatomically intermingled, a means for selective activation of these populations had been achieved.

Gore et al. used this approach to demonstrate that optical activation of nicotine-responsive and footshock-responsive neuronal ensembles in BLA elicited distinct, valence-specific, physiological responses (opposite changes in heart and respiratory rate) [24]. In addition, activation of footshock-sensitive neurons elicited freezing, a defensive response. Thus representations of USs in the BLA have the capacity to elicit valence-specific innate emotional responses.

Activity within the representation of an appetitive or aversive US in the amygdala was also demonstrated to be sufficient to drive Pavlovian conditioning if US activation was temporally paired with a CS. Photoactivation of neurons responsive to footshock could induce freezing if paired with a previously neutral auditory tone, or, if paired with a previously neutral odor, could induce avoidance of that odor. Photoactivation of neurons responsive to nicotine paired with a previously neutral odor could induce approach to that odorant [24]. Moreover, photoactivation of nicotine-responsive calls could also induce instrumental learning, as mice would learn to nosepoke preferentially to a portal paired with optical activation even in the absence of any other reinforcement. Thus appetitive and aversive neuronal ensembles in the BLA were linked causally to a variety of valence-specific behaviors: innate physiological responses, both innate and learned freezing, approach and avoidance induced by Pavlovian conditioning, and learned approach induced by operant conditioning [24].

The capacity of neural representations of USs in BLA to drive both innate and learned behaviors raises the possibility that these representations provide a link between earlier stage sensory representations of CSs and USs and the neuronal circuits that must direct valence-specific behavior itself. If this notion is correct, then sensory information about CSs must engage neural representations of USs in the BLA to direct learned emotional behavior. Gore et al. addressed this hypothesis by first labeling cells responsive to an aversively conditioned CS in the BLA. Optical activation of the cell population responsive to an aversively conditioned CS indeed elicited the expression of aversively conditioned behavior. Thus the BLA contains a representation of a CS after learning that is sufficient to direct appropriate behavioral responses [24].

In a subsequent experiment, Gore et al. showed that the expression of behavior indicative of aversive learning requires activation of a US representation in the BLA. In these experiments, the c-fos promoter drove the expression of halorhodopsin, allowing the authors to inhibit cells based on their physiological response properties [24]. Photoinactivation of shock-sensitive neurons in BLA prevented the expression of freezing in response to a footshock-conditioned tone, and it prevented the

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expression of avoidance in response to a footshock-conditioned odor. The representation of a CS must therefore normally activate a US representation in the BLA to generate appropriate behavioral responses for aversively conditioned stimuli.The US representation in the BLA can therefore be conceptualized as providing a critical link between earlier stage sensory representations of stimuli and the output pathways that mediate appropriate behavior [24]. Optogenetic interrogation of anatomical pathways originating from the BLA also indicates that neurons within the BLA mediate valence-specific behavioral responses [30–33].

Valence-specific networks of neurons in the BLA have also been identified by Redondo et al. using a transgenic approach and again exploiting activity-dependent expression of ChR2 [34]. In this study, complex stimuli comprising both a CS and a US, or exposure to a mating experience, were used to label neurons in the aversive and appetitive systems. By subsequently reactivating those cells with photostimulation of the BLA, valence-specific behavioral responses were observed in the absence of the CS, as mice avoided the context associated with aversive conditioning and approached the context paired with an appetitive experience. Moreover, consistent with electrophysiological data demonstrating that amygdala neurons preserve their valence encoding even after switches in reinforcement contingencies, reversing the contexts associated with each valence did not affect the valence specificity observed upon photoactivation of a particular amygdala population of neurons.

The new molecular approaches for identifying, marking, and manipulating neural activity in anatomically intermingled yet distinct neural circuits have propelled the field forward by providing causal evidence linking the physiological response properties of neurons to predictable and appropriate behavior. Although much work remains to understand amygdalar appetitive and aversive circuitry in greater detail, and for a broader range of stimuli, the new methodology probably corresponds to a watershed event for characterizing neural circuit function, at least in relation to relatively simple appetitively and aversively motivated behaviors.

Updating the Valence Representation in the Amygdala: Learning, Extinction, and Cognitive Regulation

Physiological data indicate that the representation of valence in the amygdala can be rapidly updated. How does this occur so quickly and flexibly? Associative learning, such as that which links a sensory stimulus with punishment or reward, is frequently assumed to arise gradually via changing synaptic weights; computational models of reinforcement learning have often worked from this assumption. The seminal Rescorla–Wagner model posits that the value representation should be updated on a trial-by-trial basis by "error signals"—that is, signals reflecting the difference between expected and received reinforcement—and recent theories [e.g., temporal difference (TD) models] have extended this model so that reinforcement learning may be described quantitatively in real time [35,36]. TD models require a neural representation of value as a function of time, with error signals being computed continuously by taking the difference in the value of situations or "states" at successive time steps. Reward prediction errors guiding value update have been shown in various areas of the brain, starting with the seminal studies of the dopamine signal in the midbrain [9,37] (see Chapter 2 for a detailed description of prediction error and dopamine signal) and extending to the medial prefrontal cortex [38–40], striatum [41–43], globus pallidus [44], and lateral habenula [45]. Neurons in this last nucleus in particular encode reward prediction error in the opposite direction compared to dopaminergic neurons [45].

Electrophysiological evidence indicates that prediction error signals probably influence processing within the amygdala. Belova et al. [23] showed that responses to reinforcement were often stronger when rewards or aversive stimuli occur unexpectedly, such as immediately after a reversal, or if the reinforcement occurs at a random time [23]. These responses differed from classical prediction error signals in that the response profile of amygdala neurons did not match the prototypical phasic, short latency response profile of neurons encoding TD errors. Moreover, amygdala neurons generally did not exhibit response modulation in relation to omitted reinforcement, a signature of neurons computing an error signal.

The modulation of neural responses to reinforcement by expectation did reveal the presence of neural processing related to both valence-specific and valence-nonspecific functions in the amygdala. Some amygdala neurons modulated their responses to an unexpected reward or to an aversive stimulus, but not to both. By contrast, other neurons modulated responses to both valences of USs when they were delivered unexpectedly. These data indicate that there exist valence-nonspecific networks in the amygdala, an observation supported by other studies [46]. Consistent with this notion, a series of studies has now linked amygdala neural activity—and targets of the amygdala—to various aspects of processing relevant for modulating spatial attention to emotionally significant stimuli (see later and [47–51]). The specific mechanisms by which the effects of expectation—and the potential processing of TD error signals—modulate neural circuit function during learning in the amygdala still await characterization at

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a more detailed level. However, at a cellular level, substantial progress has been made in characterizing synaptic plasticity during learning in the amygdala (for example, [17]).

Although our understanding of how TD errors impinge on amygdala processing during learning remains somewhat limited, much progress has been made in understanding neural circuitry related to extinction. Extinction provides a powerful means for changing behavioral responses to previously conditioned appetitive or aversive stimuli. A detailed analysis of circuitry within the central amygdala, as well as the contribution of the prefrontal cortex to extinction and its relation to amygdala function, has been advanced [52–54]. These topics have been reviewed, and will not be summarized in detail here [55,56]. Instead, we turn our attention to issues related to the cognitive regulation of emotion, a topic of considerable interest for understanding the normal flexible regulation of emotion, which does not require a process of extinction for adjusting responses to a particular stimulus.

The regulation of emotions can be extremely flexible. Responses to a sensory cue can be adjusted just by invoking a cognitive process, like the knowledge of the rules of a game. For example, in blackjack, the same sensory stimulus can be rewarding in one hand, because a player makes "21," but punishing in the next hand, because the player goes bust. The player has no difficulty adjusting emotional responses to the same card, so long as the rules are understood. The mechanisms underlying this flexibility are not well understood.

Historically, the flexible regulation of reinforcement expectation has often been studied using reversal-learning tasks. In these tasks, two stimuli and/or actions reverse reinforcement contingencies, and animals must learn these new associations. In principle, flexible adjustment of reinforcement expectation during reversal learning can involve two different sorts of mechanisms, a learning process or a cognitive control mechanism. In a learning process, each CS–US association is learned independently upon the reversal. Although behavioral training can lead to faster learning rates, fundamentally the learning about each CS–US pair is a distinct process. In a cognitive control mechanism, subjects can exploit a rule embedded in a reversal-learning task, namely that two CS–US contingencies switch at the same time. If a subject grasps this rule, then upon experiencing one CS as having switched its reinforcement contingency, a subject can infer that the other CS has switched. Two recent studies have explored neurophysiological processing in the amygdala and the prefrontal cortex during the performance of reversal-learning tasks in which subjects invoke either learning or cognitive control strategies.

Morrison et al. [57] targeted simultaneous physiological recording in the amygdala and orbitofrontal cortex (OFC), an area that has been implicated in mediating reversal learning in some (but not all) studies [58–65]. Neurons in the OFC encode positive and negative anticipated reinforcement outcomes [65–71] and have often been studied during decision-making tasks. During classical conditioning tasks, OFC neural responses are correlated with monkeys' behavioral use of information about both rewarding and aversive CSs, and positive and negative neurons in the OFC—like in the amygdala—track value in a consistent manner across the various sensory events in a trial—including the fixation point and CS and US presentations—even though those stimuli differ in sensory modality [66,67].

Morrison et al. [57] examined the OFC and amygdala neurophysiological responses while monkeys performed a task in which one CS predicted a liquid reward and another CS predicted an aversive air puff; the two CSs switched contingencies without warning during recording experiments. Behavioral evidence indicated that monkeys updated their reinforcement expectation for each CS independently upon reversal (a learning mechanism) [57]; there was no evidence of monkeys employing a cognitive strategy. Although neuroscientists have long believed that the prefrontal cortex drives reversal learning, this assertion has often been made without distinguishing between the types of strategies that might be employed and how neural processing may differ depending upon the strategy [58–62,64,65,72].

Morrison et al. [57] were able to examine the dynamics of learning in positive- and negative-valenced neurons in both amygdala and OFC when monkeys were not employing a cognitive strategy, but instead relied on independent learning about each changed CS–US association. Appetitive and aversive networks in the OFC and amygdala exhibited different learning rates, and—surprisingly—the observed differences depended on the valence preference of the cell populations in question. For positive cells, changes in OFC neural activity after reversal were largely complete many trials earlier than in positive cells in the amygdala; for negative cells, the opposite was true, as the aversive network in the amygdala learned more rapidly than the aversive network in the OFC. In each case, the faster-changing area was completing its transition around the time of the onset of changes in behavior; meanwhile the other, more slowly changing, area did not complete the shift in firing pattern until many trials after the behavioral responses began to change (Fig. 3.1).

Thus, signals appropriate for driving behavioral learning are present in both brain structures, with the putative aversive system in the amygdala and the appetitive system in the OFC being particularly rapid in

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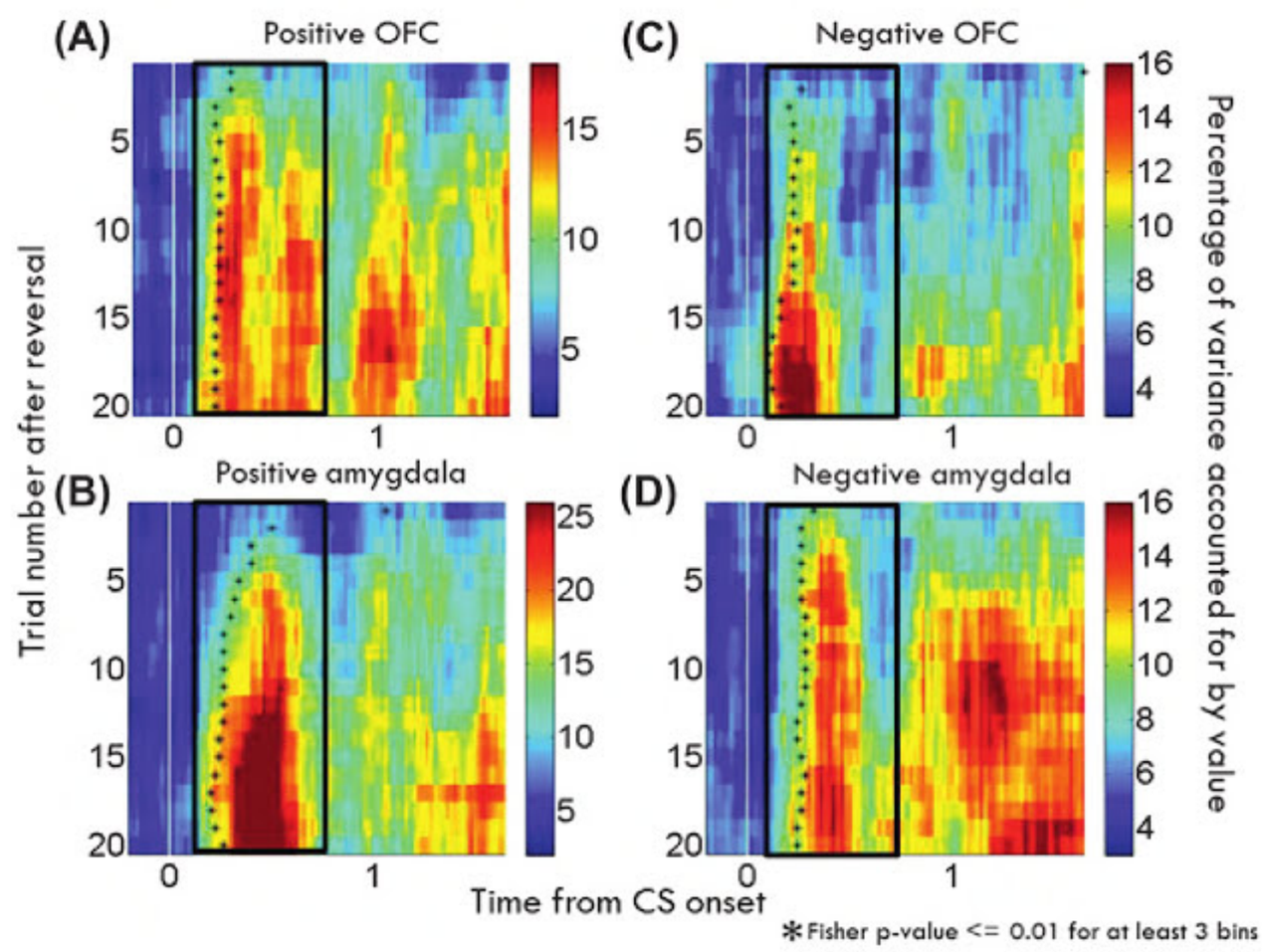

FIGURE 3.1 (A–D) Time course of changes in value-related signals in the amygdala and orbitofrontal cortex (OFC) as a function of reversal learning. For each bin, an index of the contribution-to-image value was computed by performing a two-way analysis of variance and calculating the proportion of variance accounted for by image value divided by the total variance (see Ref. [57]), and then averaged across cells. These index values are plotted as a function of trials after reversal and time from image onset (*white line*). Average contribution-of-image value to neural activity from positive value-coding neurons in (A) OFC and (B) amygdala, and from negative value-coding cells in (C) OFC and (D) amygdala. *Asterisks*, time when the contribution-of-value index becomes significant (for asterisks placed in the center of the first of at least three consecutive significant bins, Fisher $p < .01$). Bin size, 200 ms. Bin step, 20 ms. Notice the different learning rates in appetitive and aversive networks across the two brain areas. *Adapted with permission from Morrison SE, Saez A, Lau B, Salzman CD. Different time courses for learning-related changes in amygdala and orbitofrontal cortex. Neuron [Internet] 2011;6:1127–40 [cited August 23, 2014]. Available from: http://www.sciencedirect.com/science/article/pii/S089662731100643X.*

reflecting changes in reinforcement contingencies. These findings suggest that distinct sequences of neural processing lead to the updating of representations within the appetitive and aversive networks. Perhaps the faster learning response of the aversive network in the amygdala reflects the preservation across evolution of an aversive system that learns very quickly in order to avoid threats. Strikingly, however, after learning occurs, and the new CS–US contingencies are established, both populations of OFC cells—positively and negatively valenced—predict reinforcement earlier in the trial than their counterparts in the amygdala. In addition, analyses of local field potentials suggested that the directional flow of information between amygdala and OFC evolves during learning, with amygdala-to-OFC directionality being stronger earlier during the learning process. Overall, these data indicate that dynamic interactions between amygdala and OFC during reversal learning may be more complex than previously appreciated, a finding supported by fMRI data [61].

An alternative mechanism underlying flexible responses to changes in CS–US contingencies involves the application of cognitive control. Knowledge of the rules governing the environment (the rule that both CS and US contingencies switch at the same time) can allow a subject to infer the new contingency associated with one CS by first experiencing the other switched CS. Saez et al. [73] investigated the use of this type of cognitive control in the process of stimulus-value updating in changing environments. In this study, monkeys acquired and retained information about different sets of contingencies associated with the same stimulus and regulated behavior accordingly. A serial reversal-learning task was performed, in which two CS–US pairs switched contingencies many times in every experiment. Every day the monkeys would be presented with new CS–US pairs, with each set of CS–US pairs comprising a "task set." In one task set, one CS was associated with reward and the other CS was associated with nothing; in the other task set, the first CS was no longer associated with reward and the second CS was. The monkeys switched back and forth between task sets. Sometimes an additional visual cue marked the task set within a trial, but on the majority of trials no cue was present so that the monkey had to rely on memory of the task set to guide reinforcement expectation upon CS presentation.

Unlike in the study by Morrison et al. [57], in this study, probably by virtue of the serial reversals in the task design, monkeys demonstrated that they employed

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a cognitive strategy to update expectations of reinforcement expectation. Saez et al. [73] measured anticipatory licking to assay expected reinforcement. Monkeys adjusted their anticipatory licking in a switch-like manner after recognizing that reinforcement contingencies had changed. As soon as they experienced the first presentation of a CS with new contingencies, they could infer that the second CS had also changed contingencies and they adjusted their anticipatory licking. In other words, after the monkey had experienced a task set in which CS A was rewarded and CS B was not, the monkey could experience one trial in which CS A was not rewarded and then instantaneously switch its anticipatory licking for CS B. Monkeys were therefore able to generalize their knowledge of task structure (i.e., the task sets that defined two abstract contexts) immediately to new CS–US combinations and infer reinforcement accurately. This occurred even when CS–US pairings had never been experienced previously, such as on the first reversal of an experiment (CSs were novel in every experiment). Monkeys' performance on this task therefore did not derive from having extensive experience viewing the two CSs in each context. These results indicate that the monkeys had acquired and retained a "mental map," an abstract cognitive representation of the rules of the task (stimulus contingencies) and did not need to rely on relearning new associations with each reversal.

Saez et al. [73] recorded single units from the amygdala, the anterior cingulate cortex (ACC; another part of the prefrontal cortex bidirectionally connected with the amygdala), and the OFC. They used a linear decoder to analyze task-relevant signals as a function of time by considering populations of neurons collectively. The chief advantage of using a decoder is that it avoids having to select cells based on their response properties; this was important because neurons often exhibit different types of selectivity in different time windows, such as selectivity to the task set (or abstract context) during the fixation interval and reinforcement expectation selectivity during the trace interval. In addition, neurons were often observed that exhibited mixed selectivity (selectivity to multiple parameters), and these neurons could also be included in the analysis. A 2013 study identifies information provided by mixed-selectivity neurons as important for computations that may endow cognitive flexibility [74].

The linear decoder was trained to read out trial features from the spike counts of the populations of neurons recorded in each brain area. The decoder accuracy provided a single summary statistic that quantified how accurately the whole neuronal population represented information about any particular variable. Information about abstract context (task set) was encoded not only in the ACC and OFC but also in the amygdala [73]. The context signal reflected a process of abstraction, as it indicated knowledge of the task sets that defined context in the study (Fig. 3.2C). Strikingly, errors in behavior (licking when no reward was going to be delivered, or not licking when reward was going to occur) were correlated with the failure to maintain a representation of abstract context in the amygdala.

The prefrontal cortex had previously been proposed to provide a cognitive map of task space [75]. The data from Saez et al. [73] indicate that this role is not limited to prefrontal cortex; moreover, the amygdala does not merely receive gated input from the prefrontal cortex, but instead it actually holds abstract contextual information relevant to forming predictions about anticipated reinforcement and applies it to compute outcome expectations that will lead to behavioral output. This may correspond to a neurophysiological signature of a cognitive control mechanism.

The Influence of Valenced Representations in the Amygdala on Cognitive Processes

Experiments have made clear that the amygdala processes information relevant for cognitive functions beyond the regulation of valenced representations. Most prominently, one cognitive process that interacts with valence attribution is attention (see Chapter 10 on the interaction between salience and valence). Cognitive resources (attention) are typically directed toward stimuli that promote or threaten survival [76]. However, a threatening or rewarding stimulus must be identified and located to guide attention. A traditional view of amygdala function has held that amygdala neurons do not encode spatial information. Instead, the amygdala had been thought to induce arousal, a spatially nonspecific means of augmenting vigilance [77], which can then influence attention.

Peck et al. [50] explored how neural activity in the amygdala is linked to spatial attention and found that amygdala neurons often combine information about both the spatial configuration of visual stimuli and the rewards predicted by stimuli. Monkeys performed a task in which the motivational significance of visual cues modulates visuospatial attention, as measured by reaction time and performance. Amygdala neurons encoded both the spatial configuration and the reward value of motivational cues. Moreover, neural responses were also correlated with measures of spatial attention. A strong positive correlation between value and spatial selectivity was observed, demonstrating that individual amygdala neurons systematically and selectively combine information about space and reward value to signal the location of reward-predictive stimuli with both negative and positive excursions in firing rate

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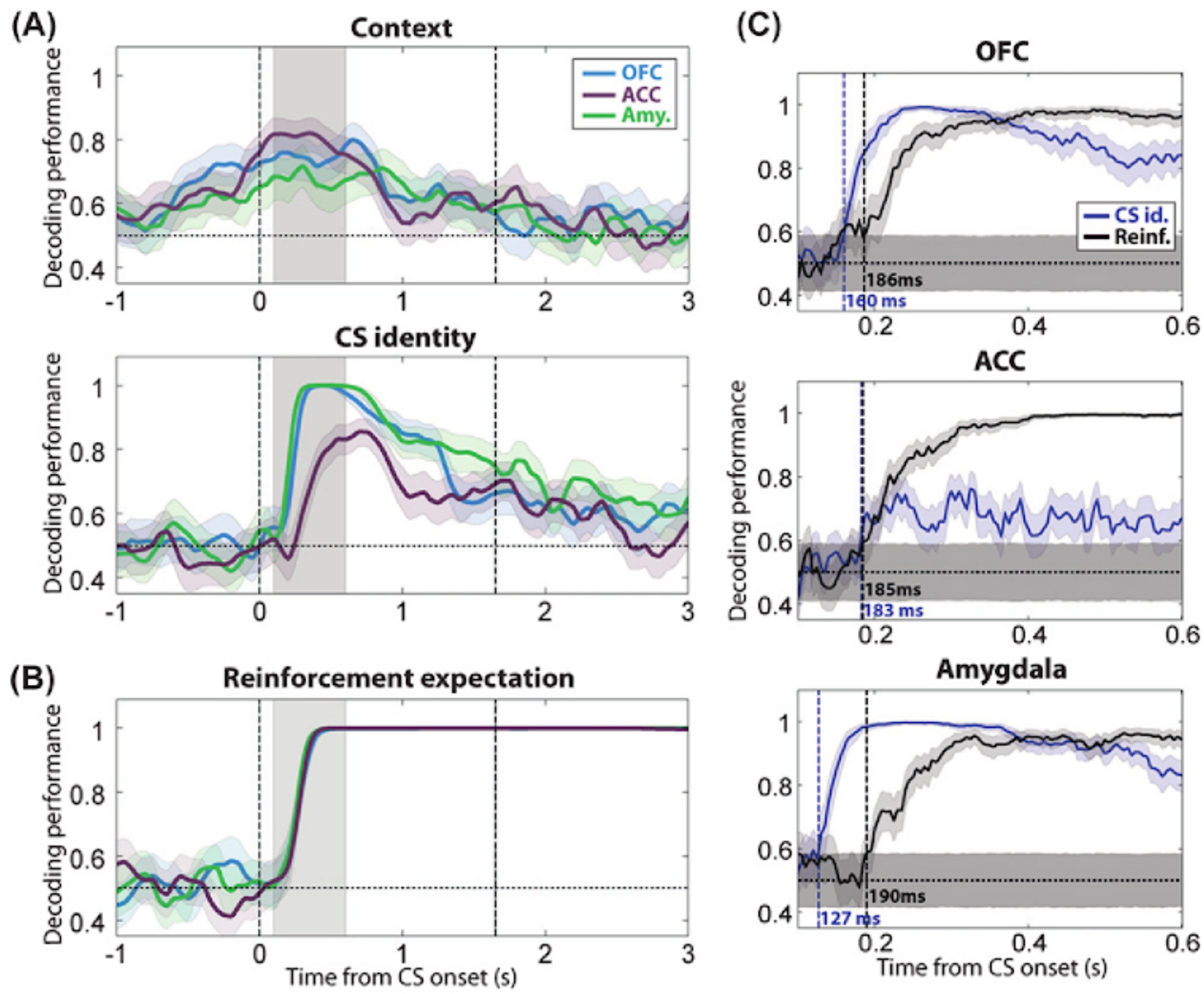

FIGURE 3.2 Population-level encoding of context and conditioned stimulus identity occurs fast enough to account for the correct anticipation of reinforcement. (A) Linear decoder performance at decoding context, and CS identity during "correct" trials. The decoding accuracy was computed on a 250-ms sliding window stepped every 50 ms across the trial for three brain areas separately: *blue*, OFC; *purple*, ACC; *green*, amygdala. The number of cells from each population used in the decoder was equalized for comparisons across areas. *Shaded areas* indicate 95% confidence intervals (bootstrap). *Vertical dashed lines* represent CS onset and earliest possible US onset. *Gray-shaded area* corresponds to 500-ms window from 100 to 600 ms after CS onset used in subsequent analyses. (B) Performance of the linear decoder at decoding reinforcement expectation. (C) Relative timing between the CS identity signal (*blue*) and the reinforcement expectation signal (*black*) in OFC, ACC, and amygdala. The performance of the linear decoder was computed on a 50-ms sliding window stepped every 5 ms across the 500-ms time window shown in (A) and (B) (*shaded area*). *Vertical dashed lines* and corresponding labels indicate the first time bin in which the decoding performance is significantly above chance level and remains above it for the 10 subsequent time bins. *Shaded areas* around chance level indicate 95% confidence intervals for the decoding performances when the two trial types (CS1 and CS2, or reward and no reward) were randomly labeled. *ACC*, anterior cingulate cortex; *CS*, conditioned stimulus; *OFC*, orbitofrontal cortex; *US*, unconditioned stimulus. *Adapted with permission from Saez A, Rigotti M, Ostojic S, Fusi S, Salzman CD. Abstract context representations in primate amygdala and prefrontal cortex. Neuron [Internet] 2015;4:869–81 [cited August 19, 2015]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26291167.*

[50] (Fig. 3.3). Moreover, the strength of the spatial signal in the amygdala is modulated by task demands, suggesting that it is related to attentional engagement [47]. In a subsequent study, Peck & Salzman. [48] extended these observations to consider how the processing of aversive stimuli is related to the allocation of spatial attention. Stimuli associated with an aversive stimulus (an air puff) attracted spatial attention. Amygdala neurons represented the spatial location of both reward- and punishment-predicting stimuli, and modulation occurred in the same direction for both types of stimuli.

In principle, neural representations within the amygdala that combine spatial information with motivational (appetitive or aversive) information might influence the degree of attention devoted to a stimulus through multiple anatomical pathways. The amygdala projects densely to the basal forebrain (BF) [78], a collection of subcortical nuclei that are the main source of acetylcholine for the brain [79]; this pathway may be a route through which the amygdala could influence dorsal stream processing, including parietal areas known to be important in attention [80]. Much like amygdala neurons, BF neurons respond selectively depending upon the spatial location and associated reward of stimuli [49].

The amygdala may also influence ventral stream processing through direct projections to visual areas [81]. This would provide a means for motivation to modulate attention and thereby improve perception at one location at the expensive of another. Indeed, the relative value of stimuli at different locations controls preferential processing to one location at the expense of others.

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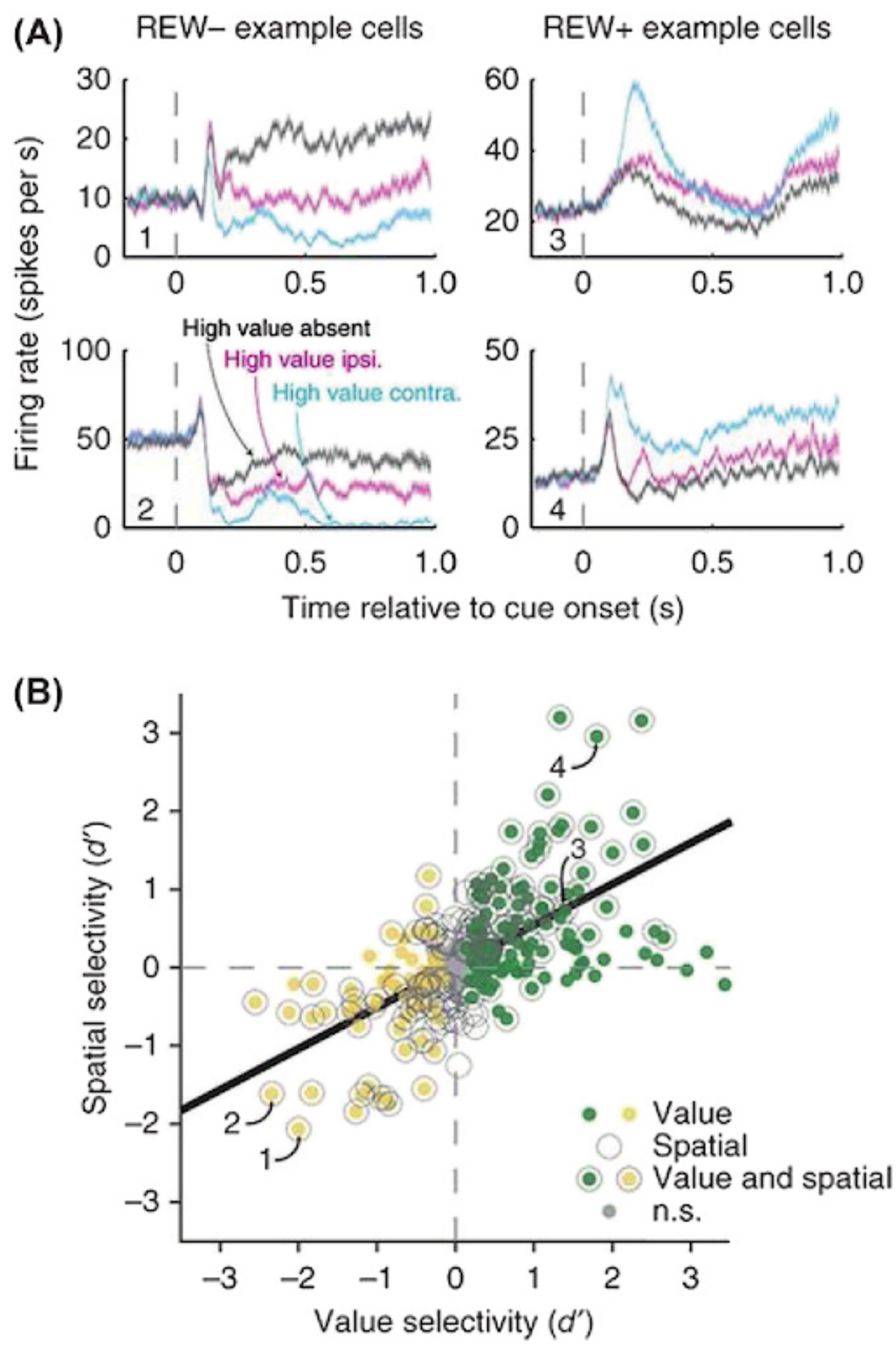

FIGURE 3.3 Amygdala neurons encode the value and spatial configuration of cues. (A) Peristimulus time histograms showing average firing rate plotted as a function of time relative to cue onset for four amygdala neurons (30-ms bins shifted by 2 ms; shading, SEM). REW− neurons map onto the aversive network, as they respond more strongly to conditioned stimuli paired with no reward than to those paired with reward. REW+ neurons by definition belong to the appetitive work, as they increase firing rate as reward expectation increases. The activity of each example neuron was significantly (bootstrap, $p < .05$) dependent on the presence and location of a cue associated with a large reward (high-value cue, which could appear ipsi- or contralateral to the recorded cell; a low-value cue appeared either in the opposite visual hemifield when a high-value cue was present or in both hemispheres). Expected reward and the spatial configuration of cues frequently had strong effects on neural responses. (B) A spatial-selectivity index was calculated comparing trials in which the high-value cue appeared contralaterally to those in which it appeared ipsilaterally. A value-selectivity index was also calculated in the same time window as for the spatial-selectivity index but comparing high-value-present trials to high-value-absent trials. Neurons that signaled the presence of a high-value cue with an increase in activity also tended to respond more when the high-value cue was contralateral. Scatter plot displays spatial-versus value-selectivity indices for each individual neuron ($n = 326$ neurons). Value-selectivity indices >0 indicate higher activity when a high-value cue was present, and indices <0 indicate higher activity when the high-value cue was absent. Spatial-selectivity indices >0 indicate higher activity when the high-value cue was contralateral; values <0 indicate higher activity when the high-value cue was ipsilateral. Symbol style indicates the significance of selectivity for each neuron (*green*, REW+; *yellow*, REW−); *black line* represents the weighted least-squares regression fit ($\beta = 0.53$, $p < 10^{-6}$). Individual amygdala neurons selectively combine information about space and value to signal the location of reward-predictive stimuli with both negative and positive excursions in firing rate. Numbers indicate data points corresponding to the example neurons in (A). *N.S.*, not significant. *Adapted with permission from Peck CJ, Lau B, Salzman CD. The primate amygdala combines information about space and value. Nat Neurosci [Internet] Nat Publishing Group 2013;3:340–8 [cited September 23, 2014]. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3596258&tool=pmcentrez&rendertype=abstract.*

Baruni et al. [51] have characterized how reward expectation can differentially modulate neural representations in one ventral stream visual area, V4. V4 has often been the focus of physiological studies investigating the neural correlates of spatial attention, and directing attention into the receptive fields of V4 neurons enhances firing rate [82] as well as gamma-band power and synchronization [83], while diminishing trial-to-trial variability and interneuronal noise correlations [84]. Baruni et al. showed that in contrast with behavior, which was controlled by the relative value of reward expectation, V4 neurons were modulated primarily by the absolute value of the stimulus associated with a receptive field stimulus. Modulation of V4 activity therefore does not necessarily predict improved perceptual performance at that location, and the modulation can be decoupled from the perceptual benefits of attention. Instead, selection mechanisms and not changes in V4 activity that reflect enhanced signal-to-noise at an attended stimulus location probably confer the perceptual benefits of attention. A ripe area for investigation concerns whether the modulation of V4 activity by absolute reward is driven at least in part by the amygdala-to-V4 connection.

CONCLUSION

Neurophysiological and molecular markers of neuronal activity have now clearly established the presence of appetitive and aversive networks within the amygdala. Moreover, optogenetic approaches have established a causal role for activity in these networks in mediating valence-specific emotional behavior. The combination of these approaches, along with appropriately designed behavioral tasks, promises to reveal in greater detail the circuit-level mechanisms within the amygdala that mediate different forms of emotional behavior. Electrophysiological studies have also begun to provide insight into how processing in appetitive and aversive amygdalar networks can be regulated by cognitive operations and how these representations may also influence cognitive functions. Continued

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efforts along these lines, potentially incorporating new tools for delineating neural circuit function, is likely to be critical for unraveling how complex neural circuit dysfunction leads to psychiatric pathophysiology.

In humans, a disruption in the neural mechanisms underlying the attribution of value, and therefore the modulation of anticipatory emotions and decision-making, can lead to maladaptive patterns of behavior. For example, addiction is commonly understood as resulting from a disruption in circuitry that processes reward-predictive stimuli and that must regulate behavioral responses to such stimuli [85]. Deficits in contextual processing can lead to interpersonal sensitivity with failures in emotional regulation such as that observed in social anxiety and borderline personality disorders [86] and schizophrenia [87]. Moreover, the inability to contextualize how stimuli and actions are related to aversive events may lead to posttraumatic stress disorder [88]. The development of transformative treatment strategies for a range of psychiatric disorders therefore probably relies on our acquiring a much more detailed understanding of neural circuitry dedicated to processing rewarding and aversive information, and an understanding of how these circuitries interact with circuitries responsible for cognitive functions [89].

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CHAPTER

4

Ventral Striatopallidal Pathways Involved in Appetitive and Aversive Motivational Processes

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Abstract

The basal ganglia are widely known to play a role in appetitive rewarding behavior. Imaging and psychiatric clinical studies have provided evidence that the basal ganglia, especially the limbic territory, also play a role in aversive information processing. Inappropriate aversive information processing could induce an anxious state, which is widely observed in a variety of psychiatric diseases. Here, we describe how the ventral striatum and the ventral pallidum, two parts of the limbic circuit in the basal ganglia, are involved in negative motivational behavior, which can be linked with the control of approach/avoidance behavior in a normal context and with the expression of anxiety-related disorders. The disturbance of this pathway would induce not only psychiatric symptoms, but also abnormal value-based decision-making.

INTRODUCTION

Every day, humans and animals must make decisions in situations or contexts that lead them to direct their actions toward events that they want to occur (approach toward appetitive stimuli) or away from events that they want to avoid (avoidance of aversive stimuli). A broad range of results from studies in humans and animals show that common and separate neuronal networks control these opposite contexts [1–7]. Although the limbic territory of the basal ganglia such as the ventral striatum (VS) and the ventral pallidum (VP) has been investigated in positive motivational behavior (approaching an appetitive goal), studies have shown that these areas are also involved in negative motivational behavior (avoidance of aversive stimuli). Neuronal representation of positive motivational behavior in these regions is obviously useful for appropriate decision-making, but that of negative motivational behavior is also useful to avoid potentially dangerous and harmful future events. For that, a process is required to discriminate conditioned stimuli (CS), which enables one to predict an occurrence of a positive or negative event in the near future, leading to anticipation of the consequences. If these processes are disturbed, this can lead to addiction (reinforced appetitive conditioning) or anxiety (excessive anticipation of negative consequence) [8,9]. The manifestation of anxiety can be observed in a variety of psychiatric disorders such as obsessive–compulsive disorders (OCDs), panic disorders, anorexia, and depression, and there is an increased demand for better understanding of the underlying neuronal mechanisms. Thus, an investigation into the role of the limbic territories, including the VS, the VP, and other regions, in aversive processes will lay the foundation for a better understanding of the physiopathology of such psychiatric disorders.

The role of the limbic territory of the basal ganglia in the processes of reward, motivation, and decision-making is now generally accepted based on a broad range of results coming from neuroimaging studies in humans and local pharmacological disturbance studies in animals, mostly rats and monkeys. In the rat, it was shown that the disturbance of the dopaminergic and opioid transmission in the nucleus accumbens induced compulsive behaviors such that decision-making and motivation were strictly directed toward food or drug-taking, two stimuli with strong reward properties [10–12]. This type of result has led someone to suggest

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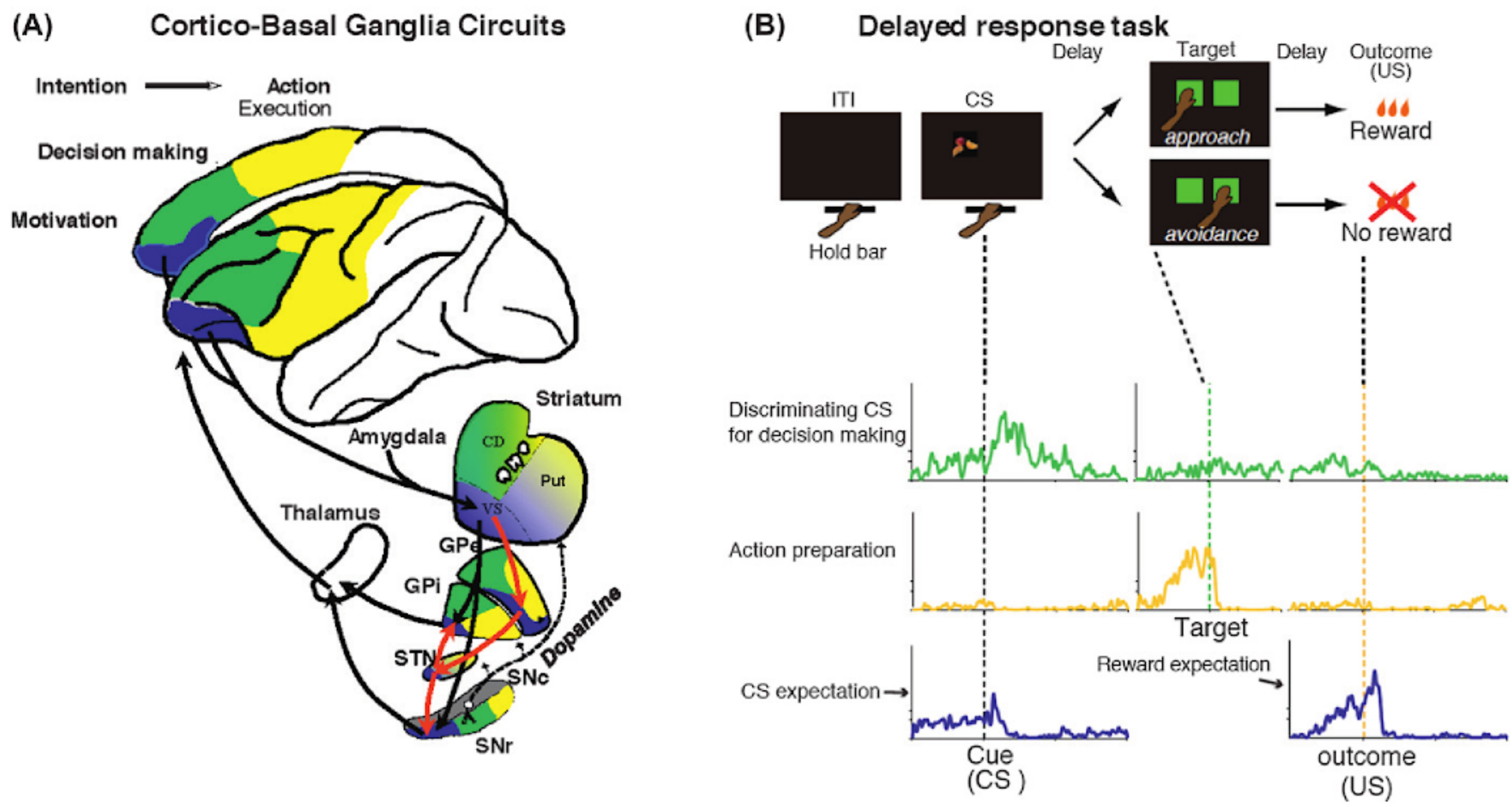

FIGURE 4.1 (A) Schematic representation of the anatomical and functional circuits of the corticobasal ganglia and (B) a schematic overview of the main forms of activity that could be observed in the striatum when monkeys performed a delayed response task. (A) The colors *purple*, *green*, and *yellow* delineate territories and activities that reflect respectively motivation, cognitive, and motor processes. Inside the striatum the territories have been characterized based on anatomical and electrophysiological investigations, whereas the territories inside the two segments of the globus pallidus (internal, *GPi*; and external, *GPe*) as well as the substantia nigra pars reticulata (*SNr*) are based only on anatomical investigation. Return projections to the cortex are illustrated only for the limbic circuit, which is presumed to be dedicated to motivation processes. The direct and indirect pathways from the ventral striatum (*VS*) to the output structure of the basal ganglia are indicated in *black* and *red arrows*, respectively. In order not to overload the picture, some basal ganglia projections are not illustrated. (B) Behavioral task in appetitive context. Subjects hold a bar to start a trial in which an appetitive conditioned stimulus (*CS*) is presented. Trials are separated by intertrial interval (*ITI*). Different examples of neuronal activities illustrated were recorded in the striatum of monkeys performing this task to obtain drops of juice as reward. *CD*, caudate; *Put*, putamen; *SNc*, substantia nigra pars compacta; *STN*, subthalamic nucleus; *US*, unconditioned stimulus.

that the VS, also called the "accumbens," functions largely as a hedonic structure. For others, it is a structure dedicated to processing the reinforcing aspect of reward, underlying the establishment of stimulus–response or context–habit associations via procedural or instrumental learning. Finally, others regard the VS as being a structure primarily implicated in the determination of the goal of an action, the "thing" that we want to obtain (e.g., food, water, sex: "positive value") or to avoid (e.g., disgusting food, pain, loss of money: "negative value"). It is also important when selecting among alternative goals and actions. In this last conception, the VS and the VP seem to function as an interface between motivation and action [13]. Over the past several years, a large number of neuroimaging studies have appeared, further highlighting these concepts and expanding the range of domains of reward and motivation processed by the VS and the VP from variables such as food [14] and sex [15,16] to financial [17] and social [18] domains. However, while results such as these may provide additional insight into the types of variables treated by the VS and the VP, they do not show how the neurons of the VS and the VP contribute to these functions. How is the basic information represented in the neuronal activity in the VS and the VP? How is this modified in a specific context of choice or decision-making? What could be the relative contribution of the VS and the VP in comparison with other cerebral structures implicated in the same network, and how do the basal ganglia interact with these cortical areas?

In this chapter, we will primarily focus on results from studies carried out on not only the appetitive aspect, but also the aversive aspect, by introducing nonhuman primate studies and human imaging studies (studies on rodents will be discussed in the next chapters). Related to this, we briefly review anatomical connections including the corticobasal ganglia, but also intrinsic connections in the basal ganglia (see also Haber's Chapter 1). Last, we will focus on the implications of the striatopallidal pathway in anxiety, which is a pathological aspect of anticipation of negative future

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events and is enhanced in uncertain states, as will be described in a later chapter by Grupe (see Chapter 30).

THE CORTICOBASAL GANGLIA FUNCTIONAL CIRCUITS: THE RELATION BETWEEN THE CORTEX AND THE BASAL GANGLIA

Within the basal ganglia and in particular within the striatum, the processing of motor and nonmotor information is carried out by the massive, topographically and functionally organized cortical projections [19–21] that provide anatomical evidence for the functional subdivision into sensorimotor, associative, and limbic territories within the basal ganglia. The basal ganglia were largely considered to comprise a motor complex in which different inputs converged to produce an output specific to the control of motor execution. At that time, the anatomical approach with classic tracers had shown that cortical regions projected into the striatum with a topographical organization in which regions could be identified based on different functional properties, i.e., the VS (limbic territory), the caudate nucleus (associative territory), and the posterior putamen (sensorimotor territory) (Fig. 4.1A). However, some cortical areas project into a similar territory of the striatum (convergence) and the reduction in the number of neurons from the striatum to the output structures of the basal ganglia, the internal segment of the globus pallidus (GPi), and the substantia nigra pars reticulata (SNr), and the large dendrites of the neurons in these output nuclei [22], strongly suggested that a large functional convergence could occur at these levels of the basal ganglia circuit before the information returned to the cortex via the thalamic relay [27,28]. In addition, only the basal ganglia return projections to the motor and the higher motor cortical areas were well described at this time, thus strengthening the view that the basal ganglia exclusively influenced motor function. It was from this viewpoint that Mogenson and collaborators [13] first suggested that the VS and the VP were perfect candidates to be the interface between motivation and action. The specific afferents of VS come from limbic structures such as the amygdala, the anterior insula, and the medial prefrontal and the orbitofrontal cortex, areas that are well known to be involved in motivational and emotional processing [23] (see also Chapter 1). Combined with the prevailing view that the principal if not exclusive output of the basal ganglia was through the motor cortex, the idea of motivation and action being integrated in the basal ganglia via the VS was compelling, and this concept continues to be expressed frequently in the literature.

An alternative view of basal ganglia circuitry can be seen to have arisen from the specific investigation of the basal ganglia output pathway(s) using rabies virus (a retrograde transsynaptic tracer) injections inside various frontal areas. This work, done by the team of Peter Strick, provided two major new pieces of information: (1) the output of the basal ganglia could project not only to the motor cortex but also to more anterior areas inside the prefrontal cortex dedicated to nonmotor functions [24,25] and (2) the output pathways to the cortex are organized in different parallel circuits where different functional domains could be processed independently [24,26]. Although Strick's team did not study the basal ganglia projections to the orbitofrontal (OFC) or the anterior cingulate cortex (ACC), their conclusions from data on other prefrontal territories strongly suggested the existence of similar closed loops in which information relative to motivation originating from the OFC and/or ACC would return to the same cortical areas after passing through the basal ganglia. In this way, as illustrated in Fig. 4.1A, the VS and the return pathways to these structures could specifically process motivational variables without necessarily exerting a direct influence on the selection or execution of action. As will be developed in the following section, this circuit could process only the goal aspect of the action (what one wants) without determining the appropriate action (which action one has to perform to obtain what one wants). As illustrated in Fig. 4.1A, a second circuit (in *green* in Fig. 4.1A) involving the dorsolateral prefrontal cortex and the caudate nucleus could be involved in cognitive processes concerning decision-making, and a third separate circuit (in *yellow* in Fig. 4.1A) involving the premotor and motor cortices together with the putamen appears to be more specifically dedicated to the preparation and execution of action. In this view, at least three corticobasal ganglia loops are implicated in the various functional processes (motivation, decision-making, and execution of action) involved in translating an intention into an action. The interaction between these different loops could happen inside basal ganglia or at the thalamic level and cortical level. Indeed, the hierarchical projection from the anterior prefrontal areas to the premotor and the motor cortex is well known [27] and these corticocortical projections could provide the link between the parallel corticobasal ganglia circuits.

THE DIRECT AND INDIRECT PATHWAYS: FROM INHIBITION OF COMPETITIVE MOVEMENT TO AVERSIVE BEHAVIORS

The striatum receives massive inputs from a variety of cortical areas; subsequently they project to the

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external segment of the globus pallidus (GPe; indirect pathway) and the GPi/SNr (direct pathway). It is well known that the neurons of the output structures, the GPi and the SNr, have high spontaneous activity (i.e., around 60 spikes/s) and thereby exert a sustained inhibitory (GABAergic) effect on their ascending targets (thalamic neurons projecting into the cortex) or their descending targets (pedunculopontine nucleus for the GPi and superior colliculus for the SNr). Hikosaka and Wurtz [28] have well demonstrated, in a series of elegant experiments using microinjections of GABA agonists and antagonists in monkeys trained to perform memory-guided saccadic eye movement tasks, that the inhibitory tone of the SNr has a direct suppressive effect on the production of saccadic eye movements. Complementary results indicate that when this inhibitory tone is suppressed or inhibited, the production of saccade is facilitated. In another series of experiments performed in rats using single-unit recording, Deniau and Chevalier [29,30] demonstrated that neurons in the SNr are directly inhibited by activation of striatal neurons. The striatal neurons can directly inhibit neurons in the SNr and thereby disinhibit the thalamic neurons under the tonic inhibitory influence of these SNr neurons. This disinhibition mechanism, whereby a series of two inhibitions has an activating effect on the target, is particularly prominent in processing within the basal ganglia. In the case of the striatal neurons involved in the direct pathway, their activation results in a "permissive" effect on their thalamic targets by this disinhibition mechanism. In contrast, activation of the striatal neurons that project to the GPe (i.e., the indirect pathway) would lead to disinhibition of the basal ganglia output structures, producing a suppressive effect on the target neurons in the thalamus. Several authors have suggested that these dual and opposing pathways could be the substrates for the role of the basal ganglia in a selection of movements [31,32]. In the motor domain attributed to the posterior part of the striatum, it has been suggested that activation of the direct pathway permits (via disinhibition) the execution of a desired motor program, whereas activation of the indirect pathway has a suppressing effect on other competing motor programs. If the same mechanism could be attributed to the VS in the domain of motivation or reward processing, the direct pathway could be engaged in the selection of a specific motivated goal, and the indirect pathway, such as the VP, would suppress other competing goals (e.g., those that are not appropriate to the current need, situation, or context). This hypothesis, based on our knowledge about the physiology and physiopathology of the dorsal striatum, is supported by studies involving local perturbations of function in the VS or the VP of behaving monkeys. Manipulations of the two pathways have revealed opposite roles in not only motor control, but also motivated behaviors [51–54].

SINGLE-UNIT RECORDING IN AWAKE ANIMALS TO INVESTIGATE THE NEURAL BASES

Most of our decisions and actions are driven by the combination of immediate or delayed expectation of reward and corresponding internal motivational factors. Numerous neuroimaging studies in humans have contributed in recent years to identifying brain areas and neural networks that could be involved in specific functional processes that drive decisions and actions in healthy subjects as well as in pathological contexts. Parts 2 and 4 of this book are dedicated specifically to reviewing these studies and their implications. One aspect of neuronal processing not accessible in neuroimaging studies, however, involves how information is represented at the neuronal level in the various brain areas identified by imaging, and thus what role each area plays in its functional networks. Knowledge about processing at the neuronal level comes primarily from animal studies using electrophysiological single-unit neuronal recording or local pharmacological modulation of cerebral circuits. This part of the chapter is dedicated to a description of the electrophysiological studies performed in the VS and the VP of monkeys in appetitive and aversive behavior.

Recording the activity of single neurons in identified brain structures of awake monkeys using inserted microelectrodes has been a classic approach for acquiring knowledge of diverse functions. Despite the tremendous advancements in the field of functional neuroimaging, electrophysiological neuronal recording retains the advantage of being a direct measure of the neuronal activity, with a notably better temporal resolution (milliseconds compared to seconds for the most advanced fMRI), which is a crucial factor when attempting to determine relationships to transient sensory, motor, and cognitive events. However, recording single neurons is a time-consuming approach, as it takes time to accumulate data from a sufficient number of neurons to have confidence that a representative sample of the structure being studied has been obtained. Even at that point, it can be argued that the sample is restricted to a relatively small proportion of neurons in that structure and that proportion could be biased by the experimental conditions. In contrast, with fMRI the entire brain can be measured virtually simultaneously in a single session; however, because of their small size (especially the VP) and relative depth, structures such as the basal ganglia have been difficult to analyze precisely in earlier fMRI studies.

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TASKS TO INVESTIGATE APPETITIVE APPROACH BEHAVIOR AND POSITIVE MOTIVATION

Approach behavior and reward-seeking, which frequently occur to achieve a goal or to obtain a reward, are fundamental positive motivational behaviors [33]. These behaviors are crucial in intake behavior such as eating and drinking [34]. To examine these behaviors, researchers use two different types of behavioral tasks, namely Pavlovian conditioning (classical conditioning) and operant conditioning (instrumental conditioning). In the former, subjects learn a CS, which is associated with an unconditioned stimulus (US). Through performing trials, subjects can predict a US (e.g., a drop of juice, one euro, etc.) from a presented CS. Subjects are required to see a CS, but not generate action. In operant conditioning, subjects learn a CS associated with a US and they have to make a decision and a response to a target presented after the CS to obtain the US (i.e., reaching a target, releasing a bar, etc.). Two delay periods are interleaved between CS presentation and the target to be reached, and between the subject's response and the US (Fig. 4.1B). If they make an incorrect response, they cannot obtain any US and another trial will start. By using this task, we can investigate the involvement of neurons in specific functions associated with behavioral events (see Fig. 4.1B).

A crucial difference between the protocols is that, whereas Pavlovian conditioning involves passive engagement in tasks, subjects have to make choices and responses voluntarily (actively engage) in operant conditioning. This difference is crucially important regarding the decision-making processes present in the operant task and not in the Pavlovian task. Fig. 4.1B shows an example of a delayed response task. To start a trial, a monkey has to hold a response bar. Then CSs associated with reward (or aversive outcome) are presented (CS presentation). After several seconds of delay, the monkey has to choose a target to obtain a reward (or avoid it if preferred). He can obtain a CS-associated outcome (US) according to his response followed by the delay period (reward delay). While monkeys perform this task, experimenters can investigate if neurons respond to behavioral events (Fig. 4.1B, lower panels). For example, before CS presentation, the monkeys expect a CS (motivational process: purple activity) and look at the CS image on the screen (attentional process: green activity). But dissociation of two possibilities would be difficult in this task because subjects are required to keep their attention on the screen and they normally have motivation to perform the tasks. To dissociate these two aspects (i.e., attention vs motivation) in neuronal activity, several different domains of stimuli that have different motivational value (i.e., positive, negative, and neutral) are used. For example, if neurons encode motivational value, neurons should show different responses between positive and negative motivational contexts. On the other hand, if neurons encode salience (potentially related to attention), neurons should show responses to both motivational stimuli [35,36]. The example of the neuron also shows CS response with phasic activity. Then a neuron could show increased activity during the first delay period while the target was being chosen, considered as preparation for action or movement-related activity (*yellow*). After the response, the monkeys wait for US delivery (anticipation period). The activity during this period would reflect anticipation of the US outcome or reward expectation (*purple*, right).

This task structure allows one to examine the characteristics of neurons in the specific territories of the basal ganglia. In the striatum and the pallidum, previous studies have shown different types of neuronal activities involved in motivated goal-directed behaviors for appetitive contexts [37–43]. A summary of the main recorded types inside the striatum is illustrated in Fig. 4.1B.

VENTRAL STRIATUM AND VENTRAL PALLIDUM ARE ALSO INVOLVED IN AVERSIVE BEHAVIORS: FIRST EVIDENCE OF LOCAL INHIBITORY DYSFUNCTION

Nevertheless, few studies in monkeys have ever taken neuronal recordings with aversive stimuli, although the aversive network has been identified in humans and animals [44]. The primary goal of previous research has been to determine the role of the VS in processing the motivational value of visual stimuli that predict primary aversive stimuli. We know from anatomical studies that the VS receives projections from cerebral structures such as the amygdala, the lateral OFC, and the insula, all of which process aversive stimuli [45–51]. Moreover, selective activation inside the central part of the VS, which produces stereotyped behaviors (an anxiety manifestation; Fig. 4.2B), induces specific activation of these three cerebral structures, which are involved in processing aversive events. Berridge has already proposed the existence of a subregion inside the VS implied in the aversive processes, based on behavioral reactions induced by pharmacological disturbances in rats [52]. MRI studies have also identified a similar subterritory in humans inside the VS that is involved in the anticipation and avoidance of aversive stimuli or unpleasant events [53,54]. We suspect that a specific territory inside the VS is dedicated to the processing of aversive stimuli. The level of heterogeneity

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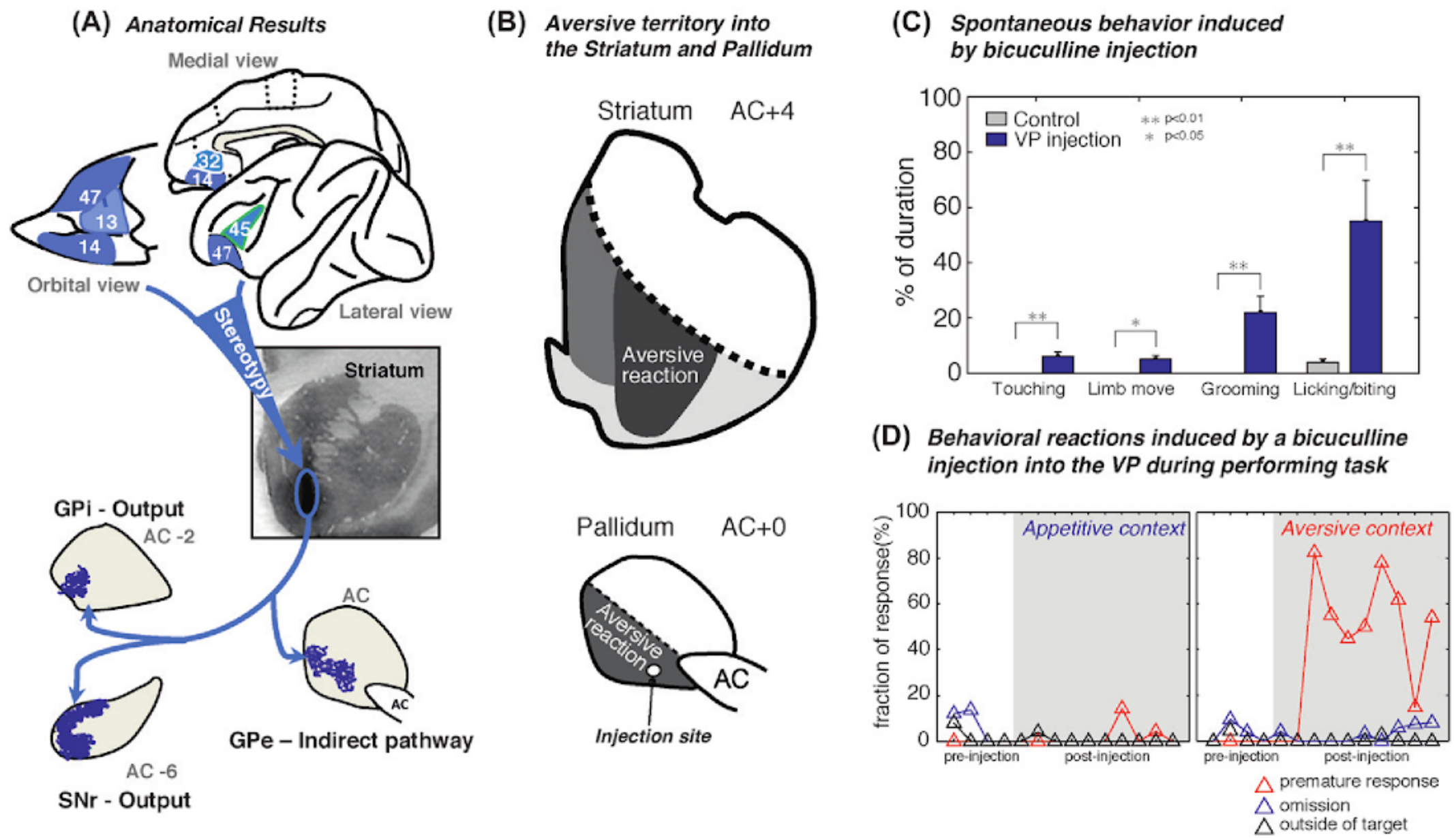

FIGURE 4.2 (A) Corticobasal ganglia circuit involved in stereotyped behaviors induced by bicuculline injection into the ventral striatum (VS) and identified by injection of biotinylated dextran amine, a retrograde and anterograde anatomical tracer *(Modified from Worbe Y, Sgambato-Faure V, Epinat J, Chaigneau M, Tande D, Francois C, et al. Towards a primate model of Gilles de la Tourette syndrome: anatomo-behavioural correlation of disorders induced by striatal dysfunction. Cortex 2013;49:1126–40, with permission.)*. (B) Hypothesized aversive territory inside the VS and the ventral pallidum (*VP*). The VS is illustrated at the level of 4 mm anterior to the anterior commissure (AC + 4), which shows the territory where negative behavioral effects were induced by bicuculline injections [63]. The VP is drawn at the level of AC 0, where the AC is still observed. The small white circle represents the bicuculline injection site. Results are shown in (C) and (D). (C) Spontaneous behavioral effect induced by bicuculline injection. The vertical axis represents the percentage of the tested duration of the behavioral patterns. Behavioral patterns are classified into touching, limb movement, grooming, and licking and biting fingers. Compulsive grooming and licking and biting fingers are the main aversive reactions induced by bicuculline injection. The *gray bars* represent control sessions (injection saline), *blue bars* indicate bicuculline injections. (D) During the task performance, bicuculline induced escape behaviors (premature responses) only in an aversive context (right). The *white zone* indicates behavioral results before injection and the *gray zone* indicates postinjection. The colored marks show each type of behavioral reaction. $^{*}p < 0.05$, $^{**}p < 0.01$. *GPe*, external segment of the globus pallidus; *GPi*, internal segment of the globus pallidus; *SNr*, substantia nigra pars reticulata.

within the VS is an important question. The heterogeneity of the VS implies that neuronal disturbances in specific territories could be responsible for various psychiatric disorders that affect the following: food intake (bulimia and anorexia), money attraction (gambling), sex activity (hypersexuality disorder), or social motivation (social phobia).

To examine the heterogeneity of the VS function, we initiated bicuculline injections into various subregions of the VS. Inhibitory dysfunction by injection of bicuculline into the VS induces stereotyped behaviors (repetitive licking and biting of the fingers and compulsive grooming), hypoactivity with loss of food motivation (reduced food intake), and sexual manifestations, depending on the injection site [55]. Subsequently, electrical stimulation of the VS induces similar effects except for sexual manifestations [56]. Stereotypy may reflect an increased anxious state because humans with anxiety frequently show similar behaviors [57–60]. Hypoactivity may reflect a reduced general motivational state or a specific loss of food motivation, which could be linked to the apathy observed in depression or loss of food motivation in anorexia [61,62]. These different aberrant activations induced from different VS territories all suggest aversive effects. Interestingly, we never observed positive effects such as enhancement of intake behaviors or motivation for performing behavioral tasks.

As for the striatum, we also manipulated pallidum activity by injection of bicuculline. The bicuculline injections induced different behavioral effects in the dorsal and ventral parts [63]. As seen in a striatal injection study, whereas injection into the dorsal part induced hyperactivity and attention deficit, injections of bicuculline into the VP induced stereotyped behaviors (Fig. 4.2B;

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increase of grooming and licking/biting fingers). Thus, the VP, like the VS, is one of the components that can produce aversive behaviors and seems to exert control on behavioral reactions to aversive events.

THE VENTRAL STRIATUM AND THE VENTRAL PALLIDUM ENCODE AVERSIVE FUTURE EVENTS FOR PREPARATION OF AVOIDANCE AND FOR CONTROLLING ANXIETY LEVEL

Unlike appetitive approach behavior and positive motivation, negative motivation and behavior to avoid harmful, fearful, or dangerous stimuli are critically important to survive in a natural environment [64]. In addition to this, aberrant processing of aversive information could lead to an anxious state. Therefore, control of these processes by neuronal activity is crucial for understanding anxiety and related disorders. Indeed, patients with anxiety-related disorders, such as posttraumatic stress disorder (PTSD) and OCD, show excessive avoidance behavior and loss of anxiety regulation [9,65,66]. Moreover, some cognitive processes are disturbed in patients with anxiety, resulting in bias to attending to potential threat information and a tendency to interpret uncertain events negatively, and these abnormal processes make them more aversive [67,68]. Thus, people with anxious traits and related disorders have been shown that their aversive information processes are abnormal and excessive.

Over the last decade, researchers have begun experiments focused on aversive information processing and negative motivation. Human imaging studies have identified the regions that process aversive motivational information, such as the ACC, the anterior insula, and the amygdala, but also the VS [54,69,70]. These areas play roles in detection of negative emotional stimuli and anticipation of negative outcomes. Human studies have identified components of the basal ganglia, such as the VS, as critical contributors to aversive as well as appetitive learning [47,53,54,69,70]. One of the pioneer works in human study by Jensen et al. [54] showed anticipation of an aversive stimulus (electrical shock on a finger), and when the subjects avoided this stimulus, the ACC, the anterior insula, and the VS were activated. More recently, common and distinct approach and avoidance networks in humans have been shown [71]. Thus, imaging studies have already shown that the brain has networks for appetitive and aversive motivational behavior, particularly in the limbic circuit.

As already mentioned, Berridge and his colleagues proposed the existence of a subregion inside the VS implied in the aversive processes, based on behavioral reactions induced by pharmacological disturbances in rats [52,72]. In addition, after the rats learned to avoid aversive outcomes (e.g., electrical shock to the feet), $GABA_A$ agonist (muscimol) injection into the VS, amygdala, and prelimbic cortex (homolog of the dorsal ACC in primates), inducing inactivation of the target region, impaired conditioned avoidance [73–76]. These results suggest that the VS plays a role in processing aversive information and learning avoidance behavior in collaboration with other cortical regions.

Although several studies have been conducted on rats, a few studies have investigated monkeys. The ACC, which projects to the VS, induces negative decision-making by applying electrical stimulation [77]. In this study, monkeys were offered outcomes and selected to approach them or avoid them by manipulating a lever. Monkeys could obtain a reward by choosing the "approach" response, but they had to receive an air puff (i.e., an aversive stimulus) before receiving the reward. The strength of the air puff and the volume of the reward were indicated by conditioned cues; therefore the parameters of the air puff and the reward varied trial by trial. Depending on the offered stimulus, monkeys approached (received an air puff to obtain a reward) or avoided (no outcome, but actually given a small reward to maintain their motivation). The stimulation of the ACC allowed the monkeys to make negative-biased decisions (more avoidance). This finding suggests that the ACC controls the decision point regarding the cost–benefit balance and regulates positive- and negative-motivated behavior.

The VP, the recipient of the VS, was also investigated in a similar way, but mainly with regard to the positive motivational context. A study of healthy human subjects showed that the VP is involved in transforming positive motivation to action [78]. In this study, the subjects were presented with an instruction that indicated a potential available outcome (money) and the handgrip power necessary to obtain it. The VP was more activated when subjects used a handgrip in higher motivational trials to obtain a greater money reward than in lower motivational trials, suggesting the involvement of positive motivational behavior. Patients with bilateral pallidum lesions showed an apathetic state, which is a state of reduced motivation [62,79,80]. On the other hand, when healthy human subjects look at disgusting food pictures, the VP and anteroventral insula are activated [81]. In rats, a VP lesion or inactivation caused an excessive disgust reaction [82]. Thus, the VP may play a role in negative or aversive information processing. However, few studies show aversive information processing in the VP of monkeys.

We have developed behavioral tasks in which monkeys were required to choose adapted behavior (approach or avoidance) faced to the value (appetitive or aversive) of the expected outcome (Fig. 4.1B). The

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monkeys were trained to perform different delayed-response tasks with appetitive and aversive outcomes (i.e., a drop of juice and an air puff, respectively). To start a trial, the monkey had to hold a lever and then a CS associated with either appetitive or aversive outcome (US) was presented on a screen in front of the monkey. After a delay period without CS, the monkey had to select one of the two targets presented on the screen. When the monkey selected the target, there were optional actions, approach or avoidance. If the monkey chose the target in the same position in which the CS was presented, he could obtain the US associated with the CS (i.e., approach). Contrary to this, if the monkey chose the opposite target, he could avoid the US and get nothing as the outcome. That meant the monkey showed active avoidance. Depending on the context of a trial (i.e., appetitive or aversive), the nature of the actions was differ (neuron 2) and a VP neuron (neuron 4) responded with transient responses to aversive CS selectively. In addition to this, we found that a number of neurons anticipated specific outcomes (see examples of appetitive and aversive anticipation in Fig. 4.3B and C, right). Interestingly, most of these anticipatory activities did not reflect the chosen action (i.e., approach or avoidance), suggesting encoding in contextual information positive and negative value rather than behavioral consequence. As in previous studies, appetitive coding neurons were found (neurons 1 and 3 in Fig. 4.3B and C). The numbers of these appetitive and aversive neurons were even and distributed equally. Although two different types of population were distributed in an intermixed manner, it is still an open question whether a specific population projects to a direct or indirect pathway. Because the VP is a nucleus of the indirect pathway, theoretically, it is possible to receive GABAergic inhibition from the VS, which is subsequently projected to the GPi or SNr (Fig. 4.3A, neurons 2 and 3). It is crucial to identify which of the two different populations projects to the GPi/SNr (direct pathway: neuron 1) and the VP (indirect pathway: neuron 2), and to what extent. Therefore, suppression activity observed in appetitive-preferring neurons in the VP might receive inputs preferentially from aversive-preferring neurons in the VS. On the other hand, neurons showing excitation responses to appetitive and aversive stimuli receive inputs from the subthalamic nucleus, whose major neurotransmitter is glutaminergic, or by suppression of inhibitory control by neighboring neurons in the VP (Fig. 4.3A, neuron 4) [83].

To further investigate the VP function on behavior, we induced local reversible dysfunction by bicuculline injection into the VP while the monkeys were or were not performing tasks (Fig. 4.2C and D). First, we

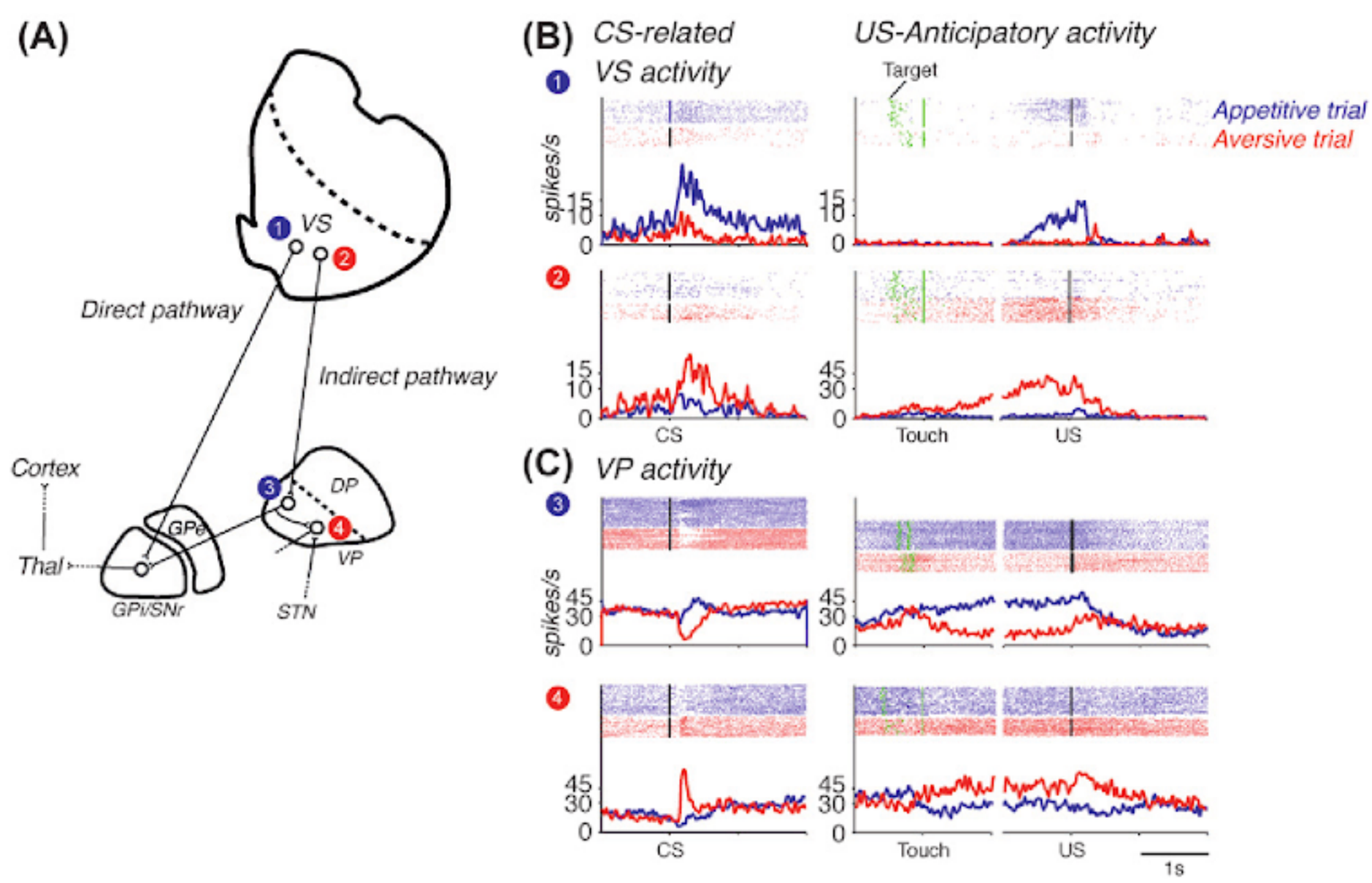

FIGURE 4.3 (A) Schematic view of direct and indirect pathways between the striatum and the pallidum. Two types of neurons in the VS project to the GPi (direct pathway) and the VP (indirect pathway). Then a signal is sent out to cortical areas via the thalamus. (B) Two examples of neurons in the VS showing response to CS (*left*: aligned on CS onset) and two examples of neurons with US anticipatory activity (*right*: aligned on screen touch and US onset, respectively). *Blue* and *red* raster and histogram represent activity in appetitive and aversive trials. (C) Two examples of the VP neurons showing CS-related and two others with US anticipatory activity [92]. The representations of raster and histograms are in the same format as in (B). *CS*, conditioned stimulus; *DP*, dorsal pallidum; *GPe*, external segment of the globus pallidus; *GPi*, internal segment of the globus pallidus; *SNr*, substantia nigra pars reticulata; *STN*, subthalamic nucleus; *Thal*, thalamus; *US*, unconditioned stimulus; *VP*, ventral pallidum; *VS*, ventral striatum.

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evaluated the spontaneous behaviors induced by the bicuculline injection (Fig. 4.2C). The VP injections induced significantly compulsive grooming and licking or biting of the fingers (typical behavior induced by a stressful situation). During the tasks (Fig. 4.2D), the bicuculline injections induced mainly the release of the response bar before presentation of the targets (premature responses: red marks). These error responses were nonadaptive behavior because an identical trial was repeated if they made an error. Additionally, the monkeys showed no movement impairment or motivational problems because they could perform trials in the appetitive context. Thus, the monkeys showed reduction of active avoidance and increase of aberrant aversive reaction in an aversive context, perhaps because they were in an excessive aversive anticipation state. These injection results support the view that the VP contributes to avoidance behavior by encoding CS and enabling anticipation of outcome. These results strongly suggest that the VS–VP pathway, an indirect pathway in the basal ganglia, greatly contributes to aversive processing and avoidance behavior in an aversive context. Moreover, an aberrant function of this pathway could contribute to generating an anxious state potentially relevant to anxiety-related disorders.

ABNORMAL AVERSIVE PROCESSING COULD BIAS DECISION-MAKING TOWARD PATHOLOGICAL BEHAVIORS

Another important issue concerning anxiety is that an anxious state could be modulated by predictable and unpredictable future events. Predictability is crucial for making plans for a subsequent action, and an unpredictable situation creates a more uncomfortable and anxious state [84]. Thus, a situation of normal predictability (certainty) enables the subject to reduce the anxiety level, whereas unpredictability increases this level. The uncertainty of the potential aversive situation enhances the anxious state, and uncertainty is associated with increased bold responses in the ACC, amygdala, and insula [85]. In humans, the anxious state can induce hypervigilance for aversive stimuli as well as excessive aversive anticipation and avoidance behaviors [47]. Hypervigilance, which is excessive fear reactions in the face of aversive stimuli, can be seen in patients with anxiety disorders like OCD and PTSD [86–89]. Presumably, the hypervigilance for aversive stimuli can induce excessive reactions even in a context that is normally perceived as appetitive or neutral. Moreover, patients with anxiety show attention bias when they are exposed to a fear or threat stimulus [86]. This abnormal perceptual processing causes abnormal value-based decision-making, especially when negative value stimuli are present. Thus, the pathological aspects of anxiety and abnormal decision-making could have a close relationship in terms of fundamental mechanisms.

CONCLUSION

We have reviewed recent studies about the neuronal basis of positive and negative motivational behavior mainly in two structures of the basal ganglia, the VS and the VP, in nonhuman primates. The comprehension of this mechanism is vital, not only to open the door for diagnostic and therapeutic developments concerning psychiatric diseases that could be caused by dysfunctions inside the basal ganglia, but also to understand the effects of neurotransmitters such as dopamine and serotonin, which could influence the activity of these structures and how they induce their therapeutic effects [90]. Gaining such understanding is a challenge that we can now master, which will greatly help us to understand some psychiatric disorders that will be discussed in the fourth part of this book. Such disorders include abnormal decision-making, which can be seen in drug addiction, pathological gambling, and anxiety-related disorders.

Acknowledgments

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CHAPTER

5

Reward and Decision Encoding in Basal Ganglia: Insights From Optogenetics and Viral Tracing Studies in Rodents

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Abstract

For the past several decades, electrophysiologists have taught us much about how the brain works by recording from neurons [1,2]. In most cases, however, we have not known what types of neuron we were recording from, or what those neurons were connected to in the rest of the brain. To truly understand a circuit, we need to record from neurons with knowledge of their cell type and patterns of connectivity. Furthermore, the ability to manipulate the activity of specific neural types provides an important means to test hypotheses of circuit function. With the advent of optogenetics, molecular techniques, and more sophisticated tracing protocols, we have finally begun to take these steps. Here we highlight advances in the physiology, function, and circuit mechanism of decision-making, focusing especially on the involvement of dopamine and its major recipient area, the striatum.

It is one of the peculiar features of most modern neurophysiology that the experimentalist seldom knows which type of neuron he or she is listening to. There is no indication of where these different sets of neurons are sending their information, let alone exactly what type of neuron they are. This is not science but rather natural history. Rutherford would probably have called it stamp collecting [3].

DOPAMINE

Decision-making is an iterative process. We list the possible choices, predict outcomes for each one, make our choice, and then experience the consequences. Finally, depending on whether the outcome was better or worse than expected, we update our predictions to make better decisions in the future. Dopamine, the neuromodulator famed for its role in Parkinson's disease [4] and addiction [5], among many other diseases, is critical for this process.

Physiology

In the mid-1990s, Schultz et al. demonstrated that dopamine-producing neurons in the midbrain of monkeys exhibit a peculiar response to reward [6] (see Chapter 2 for details). When reward is delivered unexpectedly, dopamine neurons fire a burst of action potentials. If the monkeys are taught to expect reward, however, dopamine neurons no longer respond to that reward. Finally, if an expected reward is omitted, dopamine neurons pause their firing at the time reward is expected [7]. Together, these results suggest that dopamine neurons signal reward-prediction error, or the difference between expected and actual reward. When reward is greater than expected, dopamine neurons fire; if reward is the same as expected, there is no response; if reward is less than expected, there is a suppression of activity.

This finding has been replicated dozens of times, from rodents [8–11] to humans [12]. The error signal has been shown to vary with all of the features that determine reward value, including magnitude [13–15], probability [16], timing [7,17,18], and subjective preference [19]. Furthermore, the signal develops in lockstep with behavior over learning [20,21]. When dopamine bursting is removed, either through genetics [22] or pharmacology [23–25], animals and humans show impaired cue-dependent reward learning, implying that dopamine may play a causal role in this process (see Ref. [26] for review).

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Although these findings were first reported with standard electrophysiology, new molecular techniques have allowed us to confirm and refine the prediction error model. Classically, for example, dopamine neurons were identified during recording using spike waveforms, firing rate, reward response, and other indirect physiologic features. However, these criteria have low sensitivity and specificity for dopamine identification [27], implying that previous studies may have recorded from a mixture of dopaminergic and nondopaminergic midbrain neurons. This is particularly important given the heterogeneity of the ventral tegmental area (VTA), which is primarily dopaminergic, but has substantial minorities of GABAergic and glutamatergic neurons [28]. To circumvent this issue, Cohen et al. [10] recorded from VTA in mice while using optogenetics to definitively tag neurons as dopaminergic or GABAergic (Fig. 5.1A–C). They found that dopamine neurons indeed showed phasic activations to reward-predictive cues and reward, similar to those found in nonhuman primates. Furthermore, the ability to record from identified dopamine neurons also allowed us to examine the computation that dopamine neurons perform without the risk of contamination by other cell types. In particular, Eshel et al. [29] demonstrated that reward expectation reduces phasic reward responses of optogenetically identified dopamine neurons in a purely subtractive fashion, an unusual computation in the brain but one that is consistent with classic reinforcement learning models.

In addition to phasic responses time-locked to salient events, baseline or tonic dopamine levels are thought to regulate various behaviors. For instance, tonic dopamine may regulate the vigor of responding or the pace of behavioral performance depending on the overall availability of reward [30]. Cohen et al. recorded the activity of optogenetically identified dopamine neurons in a task in which the overall value of the state was modulated over a relatively long time scale (>1 min) [31]. They found that dopamine neurons did not change their baseline firing rates depending on the state value; instead, they found that many serotonergic neurons in the dorsal raphe changed their baseline firing rates in the same task. A study in nonhuman primates made a similar finding [32]. These studies, using molecular identification of different cell types, are quickly refining our knowledge of how the neuromodulator systems interact during learning.

In contrast to the phasic activity of dopamine neurons in the VTA, GABA neurons showed a very different response: they ramped up activity from the onset of a reward-predicting cue to the time of expected reward [10]. This pattern of activity supports the idea that local GABA neurons provide dopamine neurons with an expectation signal. When reward is expected, the inhibitory GABAergic input might cancel excitatory reward input from elsewhere in the brain, eliminating dopamine neurons' response. Causal manipulations using optogenetics allowed us to test this hypothesis (see later) [29]. Note that it is only with the advent of advanced molecular techniques that we are able to dissociate intermingled cell types and assign possible functions to each one.

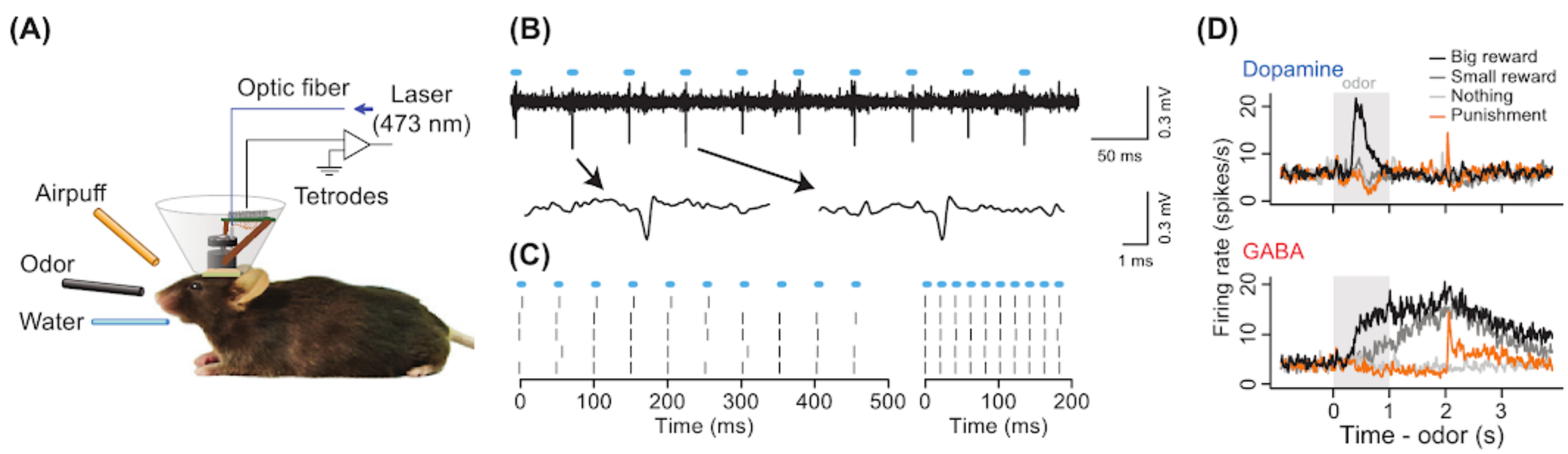

FIGURE 5.1 **Optogenetic tagging.** One of the major shortcomings of traditional extracellular recordings is the inability to identify the cell type being recorded. Here optogenetics was paired with electrophysiology to remove this limitation. (A) Transgenic mice were injected with a virus expressing the light-sensitive cation channel channelrhodopsin-2 (ChR2) and then implanted with tetrodes and a fiber optic, allowing for simultaneous light delivery and extracellular recording. Depending on the transgenic strain, ChR2 would be expressed in either dopamine or GABA neurons. (B) Voltage trace of an example identified dopamine neuron during 10 pulses of 20-Hz light stimulation (*cyan bars*). Two individual spikes are shown below. (C) Response from the same neuron to 20 (left) and 50 Hz (right) light stimulation. (D) Firing rate of one identified dopamine neuron (top) and one identified GABA neuron (bottom) during a classical conditioning task in which mice associated different odors with a big reward (black), a small reward (dark gray), nothing (light gray), or an air puff (orange). *Adapted with permission from Cohen JY, Haesler S, Vong L, Lowell BB, Uchida N. Neuron-type-specific signals for reward and punishment in the ventral tegmental area. Nature 2012;482:85–8. http://dx.doi.org/10.1038/nature10754.*

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Recording from dopamine cell bodies is only one part of the puzzle. To understand the downstream effects of dopamine release, it is also important to record from dopamine axons in target regions. Here again, new techniques have paved the way. Gunaydin et al. [33] used fiber photometry along with genetically encoded calcium indicators to explore the role of dopamine afferents in the striatum for social behavior. They implanted transgenic mice expressing a calcium indicator (GCaMP) in neurons expressing tyrosine hydroxylase (TH) with an optical fiber in the nucleus accumbens and successfully detected activity in dopamine axons while mice interacted with one another. In particular, they found that increases in VTA—nucleus accumbens projection activity predicted social interaction. This finding—specific to both the cell type of origin and the downstream target—opens up new avenues for understanding the physiology of normal behavior.

Function

Understanding dopamine function requires both readout and control. New molecular techniques have allowed us to make headway on the latter as well. Several experimenters have used channelrhodopsin (ChR2) in transgenic mice to optogenetically activate VTA dopamine neurons and examine the effects on behavior. In the first study of its kind, Tsai et al. [34] showed that mice preferred environments that had been paired with dopamine stimulation. Although previous studies had demonstrated conditioned place preference with electrical stimulation of dopamine-producing regions, this was the first experiment using selective dopamine neuron stimulation. Importantly, mice showed a place preference only when dopamine neurons were stimulated in a phasic fashion; tonic stimulation, which did not elicit dopamine transients in the striatum, had no behavioral effect. Later studies confirmed and extended these results, finding that optogenetic dopamine stimulation facilitates approach behavior in both mice and rats [35—37].

One elegant study [38] used optogenetic manipulation to test a crucial tenet of reinforcement learning theory (Fig. 5.2). In the 1960s, Kamin reported that if stimulus A already predicts a reward, then combining A with a new stimulus X fails to trigger an association between X and the reward [39]. In other words, if a reward was already fully predicted, pairing that reward with another stimulus would not cause a conditioned response. This phenomenon, called blocking, revealed the importance of prediction error. For associations to form, the outcome must be different from the expected.

We now know that dopamine neurons encode prediction error (see earlier). If this dopamine signal is indeed important for learning, then dopamine stimulation should be sufficient to reverse blocking. This is exactly

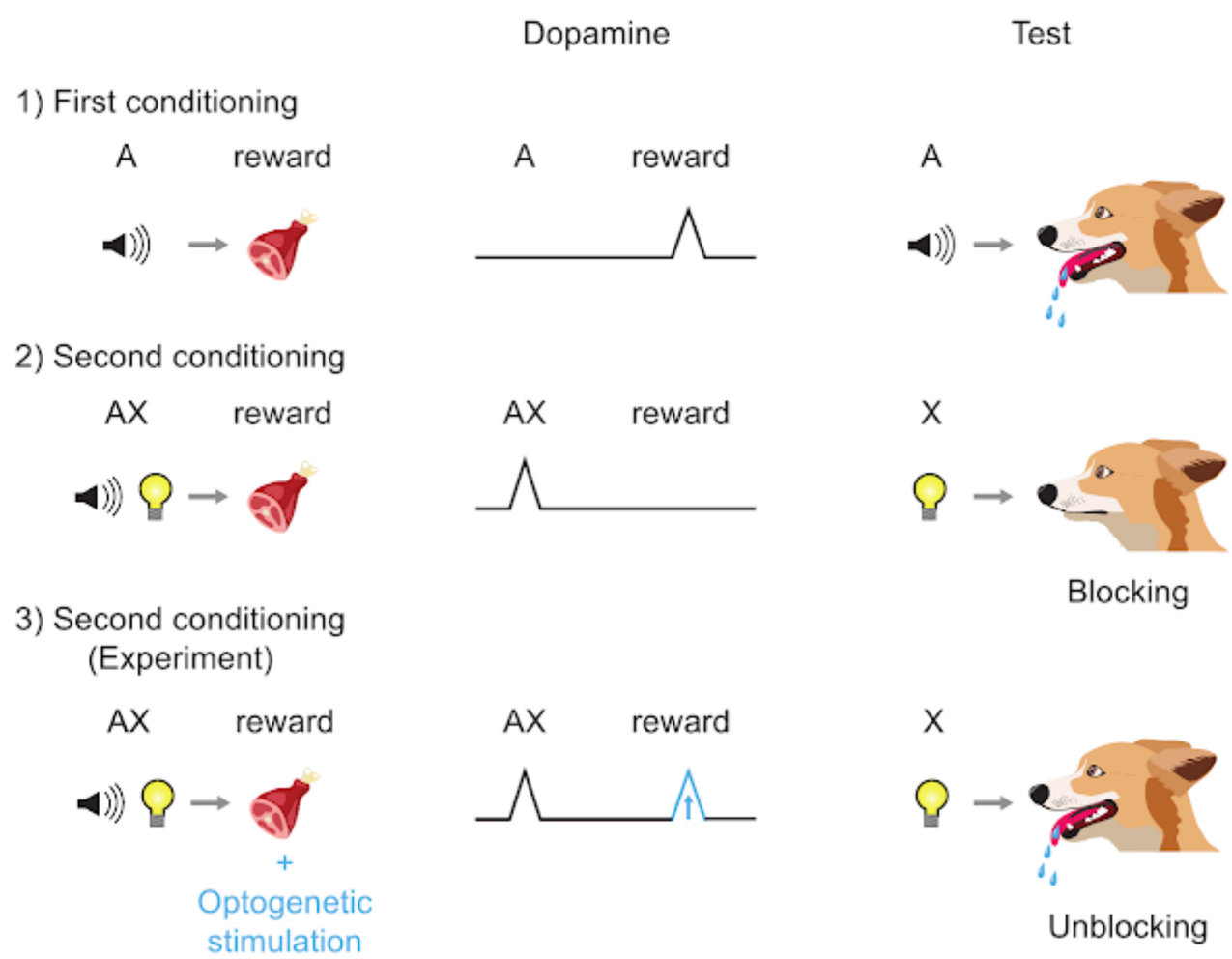

FIGURE 5.2 **The role of dopamine in blocking.** During initial conditioning, the animal learns to associate a tone with reward. After many pairings, a light is added to the tone, and this combination is paired with reward. But now the reward is fully predicted, so dopamine no longer responds to it. In the absence of dopamine, the animal fails to associate the light with the reward. However, if dopamine is artificially increased at the time of predicted reward, the animal learns the association. *Adapted with permission from Eshel N, Tian J, Uchida N. Opening the black box: dopamine, predictions, and learning. Trends Cogn Sci September 2013;17(9):430—431. http://dx.doi.org/10.1016/j.tics.2013.06.010 [Epub 2013 July, 3]. Based on the work of Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. A causal link between prediction errors, dopamine neurons and learning. Nat Neurosci 2013. http://dx.doi.org/10.1038/nn.3413.*

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what Steinberg et al. [38] found. They used ChR2 to stimulate dopamine neurons during the fully predicted reward, mimicking a prediction error. They found that such stimulation was sufficient to unblock learning, causing rats to respond to the previously blocked cue. Thus, dopamine prediction errors appear to be causally involved in associative learning. The temporal precision and cell-type specificity of optogenetics was crucial for this experiment to succeed.

Circuitry

Ultimately the goal of our field is not to understand dopamine neurons in isolation, but rather to understand the circuit in which they act. New techniques have allowed us a much better window into this circuit.

Anatomically, decades of experiments have attempted to trace inputs to dopamine neurons [40,41]. However, conventional tracing methods could not distinguish between dopaminergic and nondopaminergic neurons in the same region, and were susceptible to contamination by axons of passage. To resolve these issues, Watabe-Uchida et al. used a modified rabies virus to map and quantify all monosynaptic inputs to dopamine neurons in the whole mouse brain [42]. They found that dopamine neurons in both VTA and substantia nigra pars compacta (SNc) received direct inputs from a more diverse set of areas than previously believed (Fig. 5.3). Furthermore, although the two regions received many common inputs, there was also a topographical shift, with SNc dopamine neurons receiving more inputs from dorsal and lateral regions.

Studies have further refined the dopamine "inputome" by identifying monosynaptic inputs to subpopulations of dopamine neurons defined by their projection targets (e.g., striatum, cortex, amygdala, etc.) [43–45]. These studies show that even projection-specific dopamine populations receive inputs from many areas, and that most populations receive a similar set of inputs. There are some differences, however. Menegas et al. [45], for example, found that the ventral striatum is a major source of input to most dopamine neurons, but does not project to dopamine neurons that project to the posterior striatum. By compiling the entire list of direct inputs to specific populations of dopamine neurons, these findings provide a foundation with which to study how neural circuits regulate dopamine neuron activity.

One of the major inputs to VTA dopamine neurons are VTA GABA neurons. As mentioned earlier, these GABA neurons encode reward expectation, ramping up in response to cues predicting water reward [10]. Do dopamine neurons use this expectation signal to calculate prediction error? To find out, Eshel et al. used optogenetics to selectively stimulate or inhibit VTA GABA neurons while recording from dopamine neurons [29]. They found that stimulating VTA GABA neurons suppressed dopamine reward responses, as if reward was more expected. Furthermore, this suppression took the same arithmetic form—subtraction—as natural, cue-driven expectation. Conversely, inhibiting VTA GABA neurons increased dopamine reward responses, as if reward was less expected. Finally, bilaterally stimulating VTA GABA neurons while keeping rewards unchanged caused mice to learn new, reduced values for odor stimuli, consistent with prediction error theory. By combining recording, optogenetic stimulation, and behavior, these experiments dissected the dopamine circuit in ways that were never before possible, revealing a crucial role for VTA GABA neurons in putting the "prediction" in prediction error.

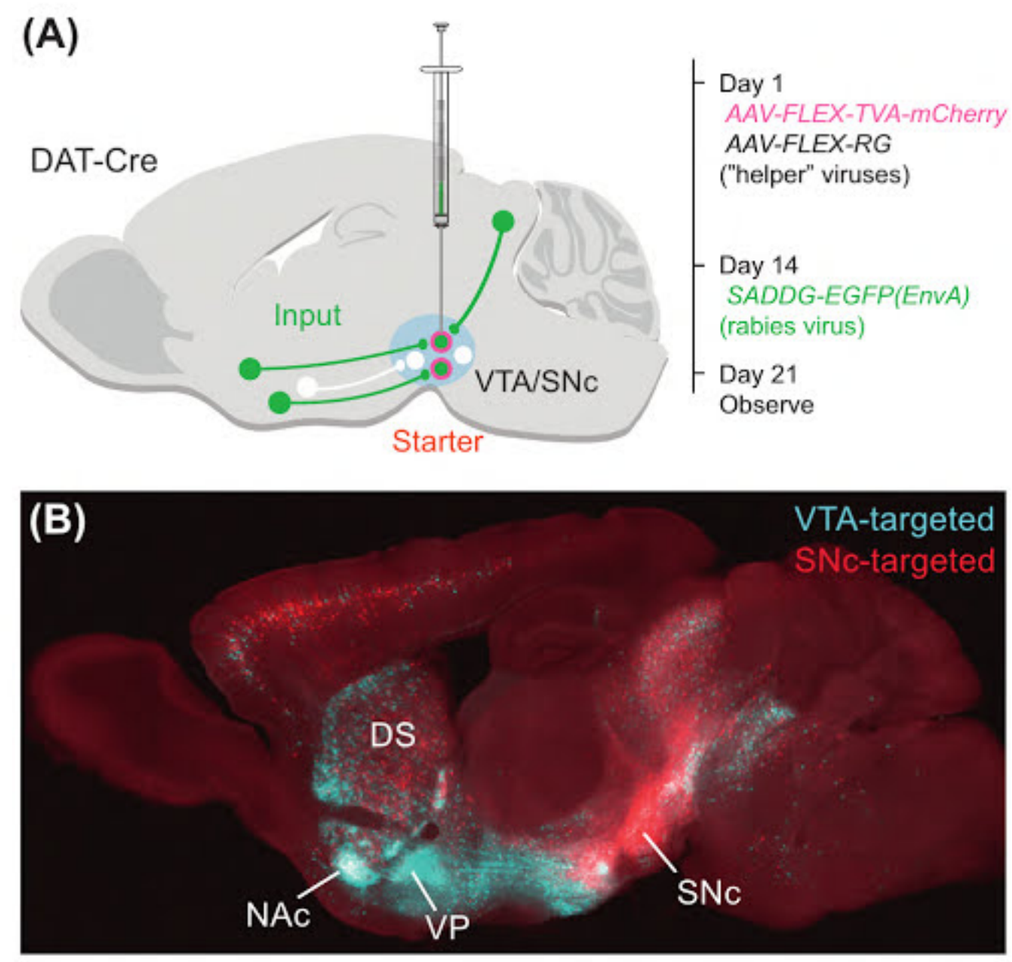

FIGURE 5.3 **Rabies virus tracing.** Compared with traditional anatomical tracing techniques, rabies virus has the advantage of labeling neurons that are synaptically connected to a population of neurons with a defined cell type. (A) Modified rabies virus was used to trace the monosynaptic inputs of dopamine neurons. The virus is pseudotyped with an avian virus envelope protein (EnvA) and therefore cannot infect mammalian cells unless they express a cognate receptor (e.g., TVA). In addition, the gene for the rabies virus envelope glycoprotein (RG), which is required for transsynaptic spread, is deleted. Therefore, transsynaptic transfer occurs only from neurons that exogenously express RG. By using dopamine transporter (DAT)−Cre mice [90], we can restrict the expression of TVA and RG proteins to dopamine neurons so that rabies virus labels only the monosynaptic inputs of dopamine neurons. (B) Sagittal slice of the mouse brain in which two types of rabies virus expressing different fluorescent proteins were injected into the VTA and SNc, respectively. Cyan neurons are monosynaptic inputs to VTA dopamine neurons. Red neurons are monosynaptic inputs to SNc dopamine neurons. The starter neurons were also labeled. *DS*, dorsal striatum; *NAc*, nucleus accumbens; *SNc*, substantia nigra pars compacta; VP, ventral pallidum; *VTA*, ventral tegmental area.

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As mentioned before, dopamine neurons also receive long-range inputs from many areas. In addition to VTA GABA input, could these long-range inputs contribute to the computation of reward prediction error? For example, many neurons in the orbitofrontal cortex signal reward expectation. One 2011 study showed that lesions of the orbitofrontal cortex impair expectation-dependent suppressions of dopamine reward responses, suggesting that the orbitofrontal cortex is a source of the reward expectation signal [9]. Similarly, previous studies in primates showed that neurons in the lateral habenula (LHb) signal reward prediction errors (RPEs), but in an opposite way compared to dopamine neurons (i.e., they are inhibited when reward is greater than expected and excited when reward is less than expected) [46]. As a result, it has been proposed that RPE is already calculated in the LHb and that RPE signals are simply relayed to dopamine neurons via inhibitory neurons in the rostromedial tegmental area, rather than being calculated locally at dopamine neurons [47]. Tian and Uchida [48] tested this proposal by lesioning the habenula and examining dopamine responses (Fig. 5.4). They found that specific aspects of dopamine RPE responses were impaired by habenula lesions. Specifically, even after large lesions of the habenula, excitatory responses to reward-predictive cues and reward were relatively unaffected. In contrast, inhibitory responses to reward omissions were impaired, even while other inhibitory responses (e.g., suppression by air-puff-predictive cues or air puff itself) were unchanged. These results suggested that the LHb is not the only source of inputs that support RPE signaling by VTA dopamine neurons. Future work will need to determine how all of the inputs dopamine neurons receive are combined to calculate RPE.

Although dopamine is classically known for its role in RPE, increasing evidence suggests that dopamine neurons are not a homogeneous population [49,50]. Rather, there is a complex system of dopamine subtypes, with differences in projections, inputs, cotransmission, and electrophysiologic and molecular features. Molecular techniques have become essential to dissect these differences. For example, Lammel et al. [51] combined slice recordings with rabies-mediated expression of ChR2 to distinguish dopamine neurons receiving inputs from the laterodorsal tegmentum versus the LHb. Those receiving inputs from the laterodorsal tegmentum tended to project to the nucleus accumbens lateral shell, and activating these inputs elicited conditioned place preference in mice. Conversely, dopamine neurons receiving inputs from the LHb tended to project to the medial prefrontal cortex and rostromedial tegmental

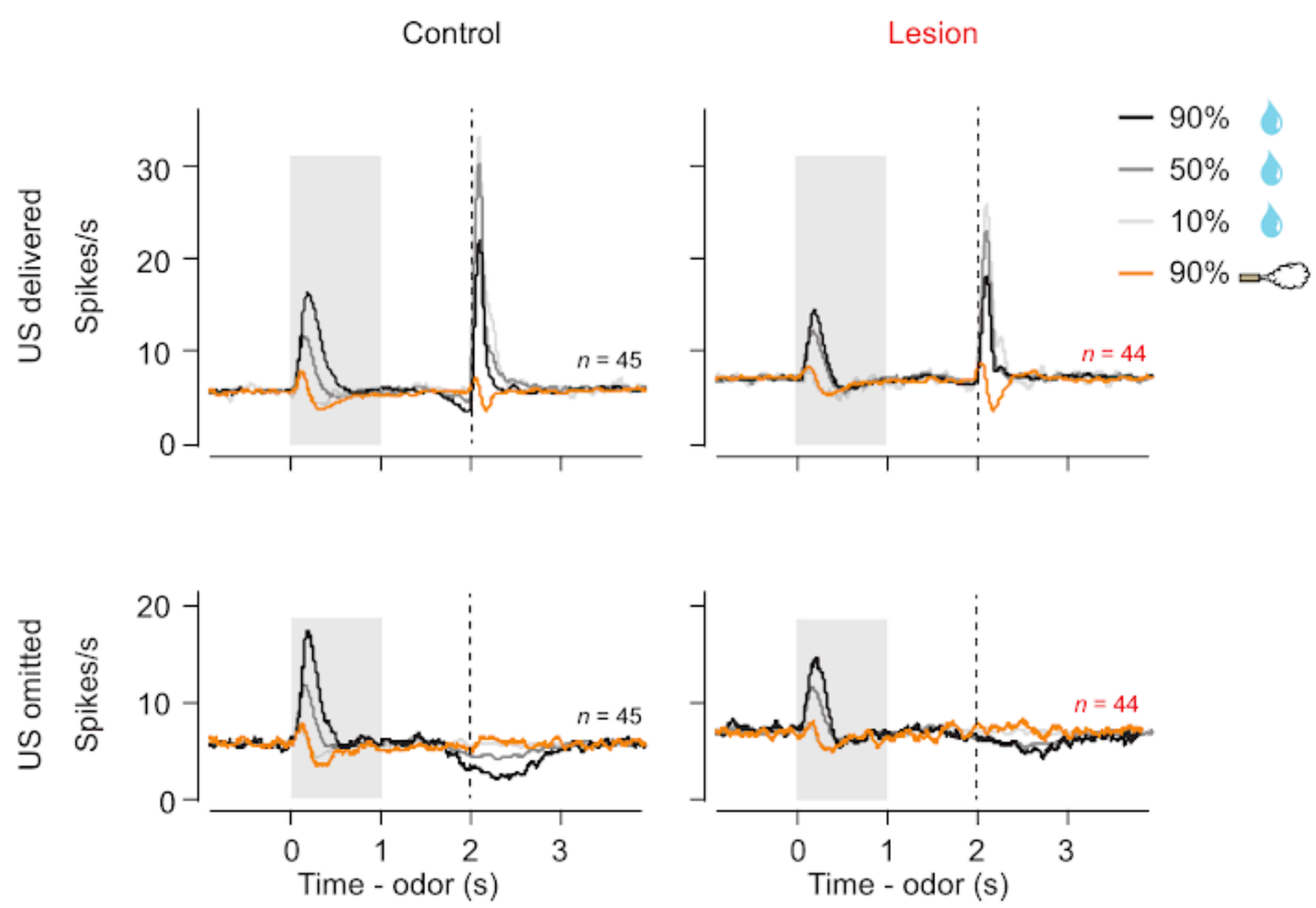

FIGURE 5.4 **Habenula lesions impair specific components of RPE signals in dopamine neurons.** Mice were trained to associate different odors with different probabilities of outcomes (a droplet of water reward or an aversive air puff). Odors were delivered for 1 s and the outcome was revealed following 1 s of delay. Dopamine neurons were identified using the optogenetic tagging method mentioned in the text. The lesion group was mice with bilateral electrolytic lesions in the habenula; the control group was mice with no operation or sham lesion. The average firing rates across all identified dopamine neurons were plotted. Compared to dopamine neurons in the control group, neurons in the lesion group tended to show weaker phasic responses. Notably, in habenula-lesioned animals, dopamine neurons were still able to encode positive prediction error, responding more strongly when reward was less predicted. However, for reward omission responses, dopamine neurons from habenula-lesioned animals were no longer able to distinguish omission of 90% reward from omission of 50% reward.

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nucleus, and activating these inputs led to conditioned place aversion. These results suggest that VTA dopamine neurons are part of multiple circuits that mediate different behaviors, and that input- or projection-specific targeting will be one important method to understand these differences. Again, it is only with advanced molecular techniques that we are now able to gain traction on the physiology, function, and circuitry underlying dopamine's involvement in decision-making and reward.

STRIATUM

The striatum is one of the major targets of dopamine axons. Historically, the striatum was considered a predominantly motor structure because of the severe motor impairments that occur when the structure is dysfunctional, for example, in Parkinson's disease and Huntington disease. Mounting evidence now suggests that the striatum also plays important roles in learning and cognitive functions, including the ability to represent and flexibly update values, learn habits and other motor skills, select appropriate actions, and regulate the vigor of responding. The striatum consists of various types of neurons expressing specific molecular markers. Over the past several years, efforts have been made to tease apart how these different neurons contribute to these important functions. In the following section, we review some of these studies, focusing particularly on those using molecular tools. More comprehensive reviews on specific functions of the striatum are available elsewhere [52–56], also see Chapter 4.

Initiating Movement, Habits, and Motor Skills

Decades of work on Parkinson's disease and the anatomy of the basal ganglia have led to various hypotheses about how the striatal circuit regulates movement initiation and action selection. More than 95% of neurons in the striatum are medium spiny neurons (MSNs), which are inhibitory projection neurons. However, there are two largely nonoverlapping subtypes of MSNs, defined by how they link to the output structures of the basal ganglia (internal segment of the globus pallidus and the substantia nigra). Direct-pathway MSNs project directly to the output basal ganglia (BG) structures, whereas indirect-pathway MSNs project to the output BG structures via intermediate targets (external segment of the globus pallidus and subthalamic nucleus). Fortunately for molecular techniques, MSNs in the direct and indirect pathways express different dopamine receptors, D1 and D2, respectively. One class of models postulates that direct-pathway MSNs facilitate movements, whereas indirect-pathway MSNs inhibit them [57,58]. Dopamine activates direct-pathway MSNs via D1 dopamine receptors, whereas dopamine suppresses the activity of indirect-pathway MSNs via D2 dopamine receptors. Thus, in Parkinson's disease patients, in which striatal dopamine is depleted, the imbalance between indirect and direct pathway activation leads to difficulty in initiating movements. A different class of models, however, proposes that coactivation of both pathways is necessary for movement [59]. For instance, direct-pathway MSNs might select the desired action, whereas indirect-pathway MSNs inhibit competing, less desired actions.

Although these models have been influential in thinking about how the basal ganglia circuit regulates movement, it has been difficult to test them directly. How does the activity of each pathway relate to action initiation? Although spike waveforms and other physiologic properties have been successfully used to distinguish MSNs from other cell types (e.g., cholinergic neurons or fast-spiking GABAergic neurons), until recently there was no way to tell whether an MSN being recorded in a behaving animal was in the direct or indirect pathway. In particular, spike waveforms and other physiological properties are indistinguishable between the two types, and identification methods based on their projection targets (i.e., antidromic spikes) were known to be ineffective. Furthermore, specifically stimulating either pathway to test its causal role in behavior was impossible. The developments in molecular tools have made it possible, for the first time, to modulate and monitor the activity of direct and indirect pathways during behavior.

In some of the first studies using molecular techniques, ChR2 was expressed in direct- or indirect pathway-MSNs in the dorsal striatum, and each pathway was activated optogenetically in freely moving mice [60,61]. These studies revealed that activation of direct-pathway MSNs increased locomotor initiation, whereas activation of the indirect pathway decreased locomotion and increased freezing. Consistent with this, optogenetic stimulation of direct-pathway MSNs increases the spontaneous activity of motor cortex neurons, whereas stimulation of indirect-pathway MSNs either decreases or causes biphasic changes in the spontaneous activity in the motor cortex [62]. Interestingly, these effects were much diminished during movement. These experiments are generally consistent with the model of the direct pathway promoting movement initiation and indirect pathway inhibiting such initiation (Fig. 5.5, model 1).

This simple see–saw model is only part of the picture, however; other studies have used molecular techniques to reveal a complicated coordination between direct and indirect pathways. To monitor the activity

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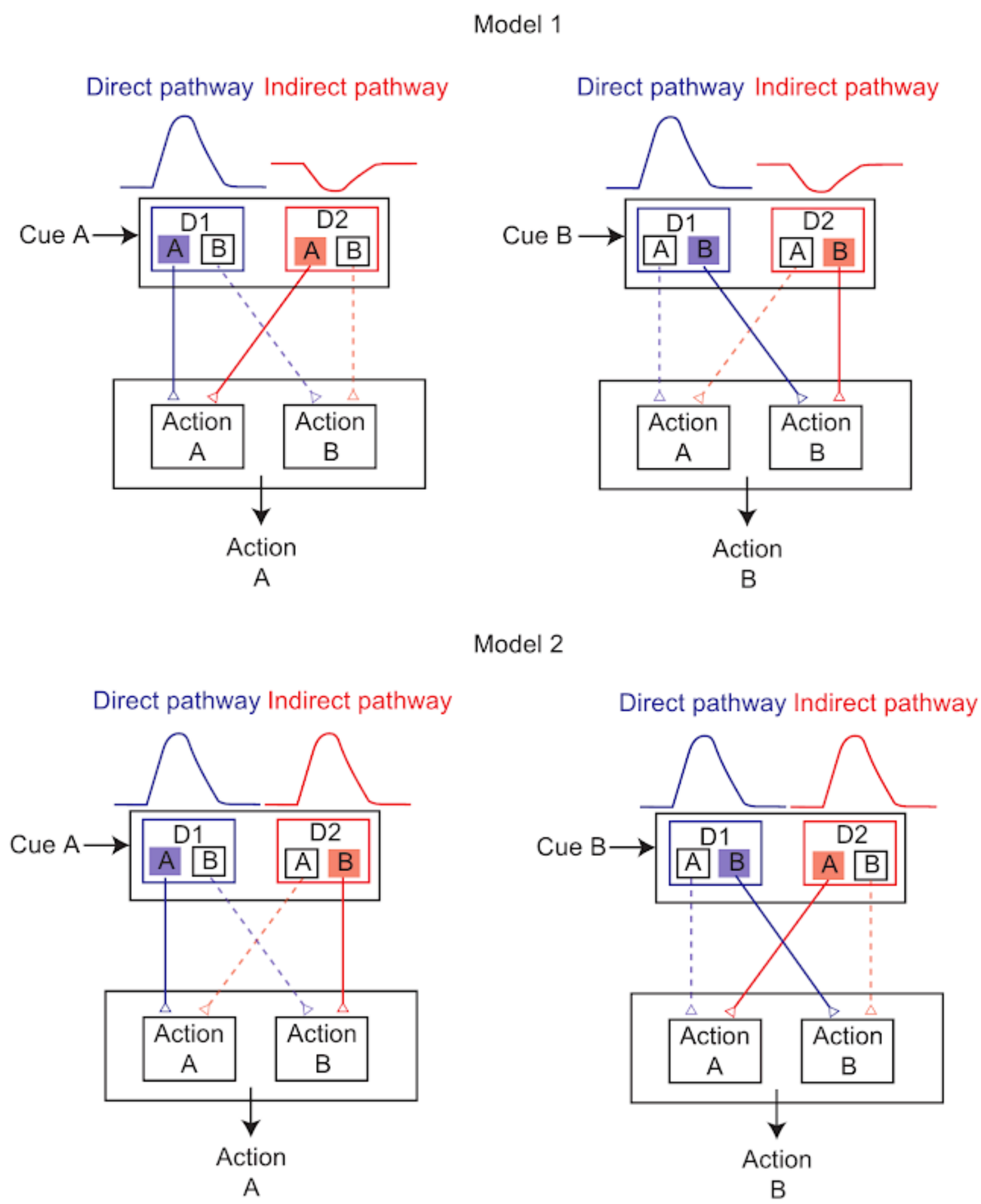

FIGURE 5.5 **Models of action selection in striatum.** Assume that to earn a reward, animals must take action A in response to cue A and action B in response to cue B. In model 1 (top), when cue A is presented, D1 neurons in the striatum are activated to promote action A and D2 neurons are inhibited to disinhibit action A. In model 2 (bottom), when cue A is presented, D1 neurons in the striatum are activated to promote action A, and D2 neurons are also activated, which suppresses competing action B. In both models, when cue B appears, a different set of D1 and D2 neurons work together to promote action B (top right, bottom right). Both models are consistent with the observations of optogenetic stimulation experiments in which activation of D1 neurons promotes movements and activation of D2 neurons suppresses movements. However, in recording experiments, D1 and D2 neurons seem to be coactivated during action selection, which suggests that model 2 might be more realistic. See main text for details.

of MSNs in each pathway, a genetically encoded calcium indicator (GCaMP3) was expressed in direct- versus indirect-pathway MSNs using transgenic mice expressing Cre-recombinase under the control of D1 and D2 dopamine receptor genes, respectively [63]. The dynamics of population activity were monitored through single optical fibers (fiber photometry). This study found concurrent activation of direct- and indirect-pathway MSNs immediately preceding the initiation of a contralateral movement. Similarly, at the single-neuron level, using the aforementioned optogenetic tagging method, Jin et al. recorded the activity of D1 and D2 MSNs in the dorsal striatum while mice executed a sequence of lever presses to get a reward [64]. Consistent with activation of both pathways during movement initiation, a similar proportion of both types of neurons were activated at the start of a motor sequence. During the execution of a motor sequence, however, D1 MSNs tended to show sustained activation, whereas D2 MSNs tended to show sustained inhibition. Finally, another study showed that balanced activation of direct and indirect pathways is necessary for proper contraversive movements, as inhibition of either pathway or both pathways disrupted contraversive movements [65]. These studies together support the model that coordinated activation of both direct- and indirect-pathway MSNs is necessary for proper movement (Fig. 5.5, model 2).

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The start/stop activities in MSNs are thought to play an important role in movement, in particular forming habits and acquiring motor skills [53,54]. But the above studies have showed that many MSNs remain active throughout the execution of habitual movements. In fact, a 2015 study showed that these activities are correlated with movement kinematics (e.g., speed or position) [66]. How different types of motor-related activities in direct and indirect pathways relate to the execution of motor behavior, in addition to initiation, remains to be further clarified.

Value Representations and Adaptive Decision-Making

In addition to the learning and execution of habitual and skilled motor behaviors, studies on the striatum have highlighted its role in flexible behavior. Accumulating evidence suggests that neurons in the ventral and dorsomedial striatum flexibly represent dynamically changing values associated with particular actions and the environment ("state"). In value-based decision-making paradigms, many neurons in the striatum modulate their activity according to the expectation of reward [67–73]. Some of these activities are related to the value of specific actions [67,70,72–74]. Furthermore, after a choice is made, some striatal neurons encode either the value of the chosen action or the actual reward received [70]. In addition to encoding the value of a specific action, some neurons in dorsomedial striatum encode the net expected reward of all available options, which is important for regulating response vigor [73].

The recording experiments mentioned earlier have indicated that MSNs represent value in various forms, but it remains unclear whether direct- and indirect-pathway MSNs make different contributions to this process. There are clues, however, from studies stimulating these two pathways during decision-making. Using a value-based decision-making task in mice, Tai et al. showed that unilateral optogenetic stimulation of D1 neurons in the dorsomedial striatum biases the animal's choices to the contralateral side, whereas stimulation of D2 neurons biases their choices to the ipsilateral side [75]. Thus, it is possible that these two populations carry inverse value functions, or might represent value in the same way, but have different mappings to behavioral output.

New molecular techniques have also begun to demystify the function of cholinergic neurons and GABAergic interneurons in the striatum. Cholinergic neurons constitute only about 1% of the total neurons in the striatum. They are known as tonically active neurons (TANs) and are characterized by 2- to 10-Hz tonic firing and wide spike waveforms. Classic primate physiology studies have shown that those neurons often show brief pauses and rebound excitation to cues associated with reward [76,77]. However, when cue values were modulated systematically by varying the probability of associated rewards, TANs did not encode the value of the cues [78], in contrast to midbrain dopamine neurons. What regulates these cholinergic interneurons during conditioning? A 2012 study using ChR2-assisted circuit mapping found that VTA GABAergic neurons selectively synapse onto cholinergic interneurons but not onto MSNs, even though the latter are the vast majority of neurons in the striatum [79]. Optogenetic stimulation of this projection caused brief pauses of striatal cholinergic interneurons, which resembles cholinergic interneurons' response to cues in classical conditioning [79].

Circuits

The aforementioned studies have begun to reveal how striatal neurons respond to various stimuli and contribute to behavior. However, how the activity of striatal neurons themselves is regulated remains less understood. The striatum receives excitatory inputs from sensory, motor, and associative cortical areas, as well as subcortical inputs from thalamic nuclei [80,81] and the amygdala. In addition, the striatum also receives neuromodulatory inputs from midbrain dopamine neurons and dorsal raphe serotonin neurons [82].

Among these inputs, synapses between cortical inputs and MSNs have been thought of as a site of learning-dependent plasticity. Learning to assign values to actions that lead to reward in a specific context is known as the credit assignment problem. It has been hypothesized that RPE signals from dopamine neurons modulate the plasticity of corticostriatal synapses, strengthening connections that promote rewarding actions and weakening connections that lead to aversive outcomes. The hypothesis is largely based on computational theories and slice physiology, and it is unknown whether it is actually implemented in striatal circuits. However, optogenetic manipulation of these circuits has provided some supporting evidence. In an auditory perceptual decision-making task, stimulation of auditory cortex neurons that are tuned to a specific frequency and project to striatum can bias animals' choices [83]. Moreover, after learning to associate a sensory stimulus with contralateral reward-seeking movements, the synapses between cortical neurons that encode this sensory information and ipsilateral striatal neurons are selectively potentiated [84]. These studies suggest that potentiation of specific corticostriatal synapses might mediate action value learning. It is still unknown what roles dopamine and serotonin might play in this process.

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New molecular tools have also been used to examine the connectivity between striatum and its inputs. There are two main types of cortical neurons projecting to MSNs, namely intratelencephalic (IT) neurons and pyramidal tract (PT) neurons. Classical anatomical studies using electron microscopy found that IT neurons preferentially synapse onto D1 MSNs, whereas PT neurons are preferentially wired with D2 MSNs [85,86]. However, using ChR2-assited circuit-mapping techniques, Kress et al. found that both D1 and D2 MSNs receive inputs from both types of cortical projection neurons [87]. To examine the whole brain inputs to D1 and D2 MSNs, two studies used rabies virus to trace the monosynaptic inputs to D1 and D2 MSNs [88,89]. Interestingly, the inputs of D1 and D2 are largely the same across cortical and subcortical areas. Thus, it remains unclear how these two types of MSNs develop their different responses; to find out, future studies will need to use molecular tools to understand the cell types that send input to each population, as well as the role of local synaptic regulation.

CONCLUSIONS

All brain functions, including reward processing and decision-making, emerge from intricate interactions among neurons. The goal of neuroscience is to probe these interactions and understand how they control behavior. In this chapter, we have reviewed advances in optogenetic, molecular, and genetic techniques, and shown how these tools have been used to dissect the circuits underlying decision-making. Discoveries are happening at an unprecedented pace; as we rapidly uncover circuit structure and function, we can be sure about one thing: that our dopamine neurons and striatum are happily engaged.

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CHAPTER

6

The Learning and Motivational Processes Controlling Goal-Directed Action and Their Neural Bases

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Abstract

Research has made considerable progress in describing the learning and motivational processes controlling goal-directed action and their related neural circuitry. Broadly this circuitry spans various regions within the corticostriatal–thalamic loop, within which specific structures mediate differentiable aspects of goal-directed learning and performance. These aspects include the acquisition of action-outcome contingencies, the encoding and retrieval or incentive value, the matching of that value to specific outcome representations, and finally the integration of this information for action selection. Information from each of the structures that mediate these processes converges on the striatum, with the posterior dorsomedial striatum in particular hypothesized to represent the neural locus of goal-directed action. Here we discuss evidence from rodent studies regarding the neural circuits mediating each of these individual processes before considering how they are integrated within the striatum for successful goal-directed action selection.

The neural bases of the learning and motivational processes that control goal-directed actions are becoming increasingly better understood. Not only are new components of this neural network increasingly being identified, but the exact nature of the unique role played by each structure within this network, as well as the interactions between them, is becoming better recognized. As a consequence, a clear picture of how the brain encodes and expresses goal-directed learning is beginning to emerge. In this chapter we will separate these processes into several key psychological capacities and explore the distinct neural bases of each. We will then examine how these individual structures and circuits interact to form the larger neural system that underlies goal-directed action.

As has been made clear previously, an action is considered to be goal-directed if its performance respects: (1) the current value of its outcome and (2) the extant contingency between that action (A) and its outcome (O) (cf. Ref. [1]). In contrast, reflexive actions or habits are controlled by antecedent stimuli (S) rather than their relationship to, or the value of, their consequences and, as such, tend to be relatively inflexible or automatic. Although there is a rich literature concerning the behavioral and neural bases of habits, this chapter will focus solely on evidence from goal-directed actions particularly from studies in rodents.

The behavioral procedure most commonly used to determine whether an action is goal-directed, and the one that will be primarily relied on here, is outcome devaluation. Typically, animals are first trained to perform an action, such as a lever press response, to obtain an outcome, such as pellets. The value of that outcome is then reduced either by outcome-specific satiety (induced by free consumption of the outcome) or by taste aversion learning (in which the ingestion of the outcome is paired with illness induced by an injection of lithium chloride) (cf. Ref. [1]). If responding is primarily goal-directed, the animal should subsequently reduce its propensity to perform the action previously associated with the now-devalued outcome, in comparison either to alternate actions earning nondevalued outcomes or to animals that did not receive the devaluation treatment. Importantly, testing occurs in the absence of outcome delivery (i.e., in extinction) so that any feedback that could be gained from experiencing the outcome is not available. This ensures that the animal must rely on its knowledge of the A–O contingency, as well as its ability to retrieve the specific

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outcome of its actions—including its current value—to perform appropriately and reduce the performance of the now devalued action relative to other actions.

There are a number of psychological phenomena that underlie goal-directed action, specifically: the encoding of the A–O contingency, reward or incentive learning, outcome-specific retrieval, and action selection and initiation in the context of goal-directed performance. These four phenomena will be described later along with current evidence as to their neural bases. Generally, at present, A–O encoding is thought to depend primarily on the prelimbic cortex (PL) in rats (homologous to the medial frontal/anterior cingulate cortex in humans), and probably involves connections with the mediodorsal thalamus (MD) and dorsomedial striatum (DMS). This learning is influenced by an incentive learning process [2] via which the incentive (or reward) value of the outcome is altered largely by virtue of the motivational state of the animal when contact with that outcome occurs. Incentive learning processes are thought to rely on structures connected with the PL, the MD, and the DMS such as the basolateral nucleus of the amygdala (BLA) and the insular cortex (IC). Once encoded, the incentive value of the outcome is matched to a broader mental representation of the outcome, including all its sensory-specific characteristics, to drive goal-directed responding. Recent data suggest that, in the absence of the physical outcome, outcome-specific retrieval and attendant reward processing depend on the medial portion of the orbitofrontal cortex (mOFC). The mOFC, IC, and BLA all project strongly to the DMS but perhaps even more densely to the ventral striatum, particularly the nucleus accumbens (NAC) core, which is known to control the performance of goal-directed actions. The posterior region of the DMS (pDMS; homologous to the anterior caudate in humans) appears to be uniquely involved in both the learning and the expression of goal-directed actions, suggesting that the information provided by each of these other structures must converge on the pDMS or on the immediate circuits controlled by the pDMS and that constitute the neural locus of goal-directed action. This chapter will first examine the neural bases of each of these psychological phenomena separately and then examine how they interact as part of the broader network with a focus on the convergence of information on the pDMS to ultimately control goal-directed actions.

LEARNING "WHAT LEADS TO WHAT": THE NEURAL BASES OF ACTION–OUTCOME LEARNING

The acquisition of instrumental responding depends on encoding the relationship between the action and the outcome (A–O). There are now several lines of evidence that suggest a specific role for the PL in the acquisition, but not performance, of goal-directed actions. The role of the PL in acquisition was first demonstrated by Balleine and Dickinson [1], who examined the effects of pretraining excitotoxic PL lesions on a variation of the outcome devaluation procedure described earlier. Specifically, rats with either sham or excitotoxic lesions of the PL were trained to either press a lever or pull a chain for food pellets or a starch solution, respectively. Prior to testing, the rats were prefed either the food pellets or the starch solution to devalue that particular outcome by way of specific satiety. On a subsequent extinction test rats with sham lesions displayed sensitivity to outcome devaluation by selectively reducing the action that had been paired with the now devalued outcome relative to the action paired with a still valued outcome. By contrast, rats with PL lesions were insensitive to devaluation and performed both actions similarly on testing. This finding is robust and has been replicated several times [3,4]. However, these results contrast with the results of "reinforced" tests that are conducted in the same manner as the outcome devaluation test previously described except that each action delivers its related outcome. In these instances, PL lesions spare sensitivity to outcome devaluation [1,3]. This finding is important in demonstrating the specificity of PL involvement in A–O learning by ruling out alternate explanations such as an inability to encode changes in value or discriminate between levers or outcomes. Further experiments have suggested that this role for PL is limited to the acquisition of goal-directed actions but not their performance. For example, Ostlund and Balleine [5] found that, even when tested in extinction, rats that received posttraining PL lesions were as sensitive to outcome devaluation as sham controls.

A separate line of evidence showing that PL lesions abolish contingency degradation performance further supports the role of the PL in A–O learning [1,3]. Specifically, although outcome devaluation performance provides evidence of A–O contingency knowledge, intact degradation performance provides specific evidence that the experimental subjects are capable of encoding the causal relationship between the action and the outcome. For example, Balleine and Dickinson [1] again trained hungry rats to perform two actions (lever press and chain pull) for two separate outcomes (food pellets and starch solution). At the end of instrumental training each action earned each outcome with a probability of .05. In the next stage of the experiment, one of these outcomes was also delivered with a probability of .05 in each second that no response was recorded. Thus, in any one second of the session, the probability of receiving that specific outcome was equal, whether or not its associated action was performed. Importantly,

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this procedure maintains contiguity between the action and the outcome, because each action is rewarded at the same rate, but the causal efficacy of the action is degraded. This typically results in a reduction in the performance of the degraded action relative to an alternate, nondegraded action that continues uniquely to predict its outcome. Indeed, Balleine and Dickinson [1] demonstrated this precise result in sham animals, but found that animals with PL lesions reduced the performance of both actions. Corbit and Balleine [3] conducted a similar experiment and again found insensitivity to degradation. In that study the rats were found to increase performance on the degraded relative to the nondegraded action. This pattern of results was revealing; further experiments suggested that, although the PL rats clearly lacked the ability to learn the A–O associations necessary for normal degradation performance, their ability to recognize the outcome as a discriminative stimulus (rather than as a goal) was intact [3]. This means to say these rats retained the ability to retrieve a specific action based on the outcome, via an O–A association, resulting in increased performance on the degraded relative to the nondegraded action; the free outcome delivery acting to drive responding on its associated action. Consistent with this explanation, when animals were given a choice lever test in extinction, rats with PL lesions chose each lever to a similar degree, suggesting that, when the outcome was not available, neither O–A or A–O associations were accessible to PL-lesioned animals.

Lesions of the MD, a structure that has strong and reciprocal connections to the PL, have been found to produce a similar pattern of results. Specifically, Corbit et al. [6] found that excitotoxic lesions of the MD abolished outcome devaluation performance (although not on reinforced tests) and contingency degradation using designs similar to those described earlier. Later, Ostlund and Balleine [7] further demonstrated that, like the PL, posttraining MD lesions spared outcome devaluation, implying that this structure also plays a role in the acquisition but not the expression of A–O associations.

The similarity in the results produced by PL and MD lesions in these tasks, as well as the heavy interconnections between these regions, led Bradfield et al. [8] to examine whether a disconnection of these regions would also produce a deficit in outcome devaluation performance. This disconnection was complicated by the fact that not only does the PL project ipsilaterally to the MD, but also there are significant contralateral projections. To overcome this we employed a novel surgical procedure that was successful in disconnecting the contralateral PL–MD projections, illustrated in Fig. 6.1 ([8], see particularly Fig. 3 in that paper). This procedure consisted of performing an electrolytic lesion of the genu of the corpus callosum (CC), and injecting fluorogold into the MD in one hemisphere. We then examined the pattern of labeling in the PL contralateral to the injection site and found that, relative to controls, the amount of labeling was almost completely eliminated, suggesting that these projections had been severed [8]. We then conducted a behavioral experiment using electrolytic CC lesions in combination with sham, ipsilateral, or contralateral excitotoxic lesions of the PL and MD. This procedure ensured that the sham group had intact ipsilateral PL–MD pathways in each hemisphere, the ipsilateral group had an intact PL–MD pathway in one hemisphere, and the contralateral group had no intact PL–MD pathway in either hemisphere. Using procedures similar to those described, we found that only

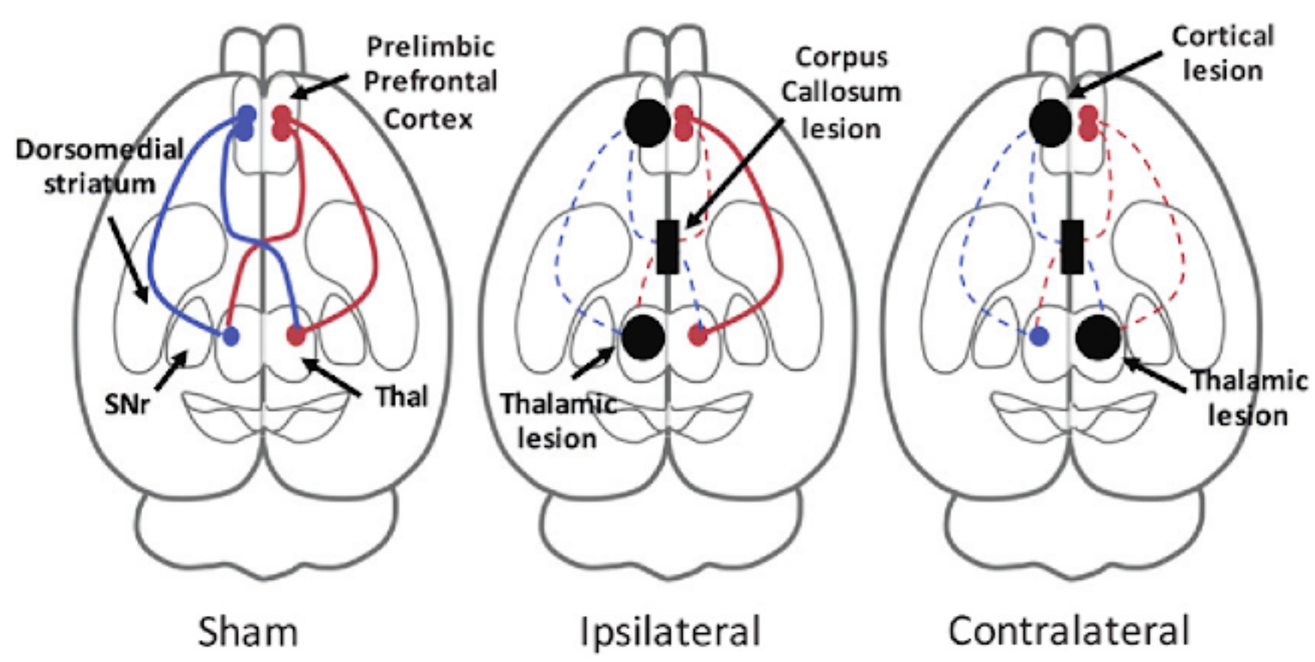

FIGURE 6.1 **Prelimbic cortex–mediodorsal thalamus disconnection.** Summary of the hypothesized influence of unilateral neurotoxic lesions of the prelimbic prefrontal cortex and the mediodorsal thalamus plus electrolytic lesion severing the crossed connections in the corpus callosum. Groups had no damage (sham); damage to the two structures ipsilaterally, leaving only one intrahemispheric connection intact; and damage contralaterally, severing all intra- and interhemispheric connections. Only the last manipulation is predicted to abolish the acquisition of goal-directed action. *SNr*, substantia nigra pars reticulata; *Thal*, thalamus.

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the contralateral group was impaired in their outcome devaluation performance but that their discrimination between actions and outcomes was intact.

Although these studies suggest a role for the MD in goal-directed learning, they appear to contradict several other studies that have failed to find an effect of MD inactivation on outcome devaluation. For example, Pickens [9] described two relevant experiments, one in which MD lesions abolished outcome devaluation performance, and another for which performance was intact. The author suggested that MD lesions might impair outcome devaluation only when rats had to alter their strategy within a task: the rats that showed the impairment had previously experienced a Pavlovian devaluation task, whereas the rats that showed no impairment had not. However, there are a number of other methodological differences between this study and the studies that did find effects of MD lesions. In particular, Corbit et al. [10] and Bradfield et al. [8] employed two instrumental actions that earned two outcomes and examined devaluation within subjects by devaluing one outcome that was prefed to satiety. Pickens [9], on the other hand, employed only one action and one outcome and compared outcome devaluation performance between subjects that had received lithium chloride injections either paired or unpaired with the outcome. Although it is not clear which of these differences could account for the different results, it would be of future interest to assess whether MD involvement in the acquisition of A–O learning is limited to situations in which devaluation is assessed in choice.

There is another study, however, that used parameters similar to ours that also failed to find an effect of MD inactivation on outcome devaluation. Parnaudeau et al. [11] used the inhibitory hM4Di designer receptors exclusively activated by designer drugs (DREADDs) paired with intraperitoneal injections of clozapine-*N*-oxide (CNO) to inactivate the MD during instrumental training or outcome devaluation testing, and failed to find an effect of either. Like our prior studies [7,8,10], Parnaudeau et al. [11] also trained two instrumental actions to predict two outcomes and examined devaluation within subjects using sensory-specific satiety. We suspect, therefore, that the reason for the discrepancy might lie in the use of DREADDs versus permanent lesions. First, the extent of the DREADDs transfection reported by Parnaudeau et al. does not appear to be as extensive as the lesions reported by Balleine and colleagues [7,8,10], particularly in more caudal sections. Second, in a prior report, Parnaudeau et al. [11] found that the administration of CNO in awake mice induced a decrease in the firing rate of only 40% and that decrease was observed in only a third of MD neurons. Although this appeared to be sufficient to produce deficits in a number of other cognitive tasks, perhaps it is not sufficient to produce a deficit in outcome devaluation in particular. Finally, the outcome devaluation effect in the group that received CNO during instrumental training—the group for which we might expect an impairment—does appear to be smaller than that observed in the control group, particularly in the first 2–4 min of the test. Although not significant, it is possible that a more complete inactivation might allow the effect to reach statistical significance.

HOW REWARDS ARE FORMED: NEURAL BASES OF INCENTIVE LEARNING

Incentive learning constitutes another process that contributes to the production of goal-directed action. Demonstrations of this effect have revealed that, contrary to the predictions of early researchers [12], alterations in motivational state (or "drive") are not sufficient to alter instrumental responding. Rather, the incentive value of the outcome must first be altered, and this is achieved through consummatory contact with the outcome within a particular motivational state, known as the incentive learning experience [17].

The earliest direct evidence for this effect as it relates to instrumental responding came from a series of experiments conducted by Dickinson and Dawson [13] in which they trained rats to press a lever and pull a chain, with one action earning a food pellet and the other a liquid sucrose solution. When tested on the two actions thirsty, for the first time, the rats failed to show any difference in performance of the two actions. If, however, prior to this test, the rats were allowed to drink a little of the sucrose solution or to eat a little of the food pellets when in the thirsty state, then, on test, they preferred the actions previously trained with sucrose relative to the other action. Balleine [2] extended this finding by examining changes in food deprivation. For the first of these experiments rats were food deprived, and half were exposed to the target food (either a food pellet or a maltodextrin solution) in the deprivation state, and half were not. All rats were then returned to free food and trained to lever press. For the final testing period, half of the rats that were preexposed to the target food and half of the nonpreexposed rats were again made hungry, then all rats were tested for their propensity to press the lever. Interestingly, in this test, only the group that had previous consummatory contact with the target outcome in a deprived state and were later tested in that state increased their instrumental responding. The group that was tested in a deprived state but not preexposed to the outcome in that state responded at levels that were indistinguishable from those of nondeprived controls. Together with that of Dickinson and Dawson [13], this finding demonstrates that in the absence of

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any incentive learning, shifts in motivational state are insufficient to influence instrumental responding. Rather the rats have to learn about the value of an outcome in a new motivational state before that value can influence performance.

Incentive learning is central to the production of goal-directed actions because it regulates the incentive, or reward, value of the outcome, as per the first of the "goal-directed" criteria outlined above. Indeed, all outcome devaluation procedures directly rely on incentive learning. During training animals usually learn to perform the instrumental actions in a deprived state, increasing the incentive value of the associated outcomes. However, if devaluation occurs by way of sensory-specific satiety, the value of the outcome loses value over the course of prefeeding as consummatory contact occurs in an increasingly sated state. Likewise, if taste aversion learning is employed, it has been demonstrated that the animal must have consummatory contact with the target outcome after its pairing with illness to have any effect on responding [14,15,16]. The current view of the structure of incentive learning is presented in Fig. 6.2A. Briefly, the sensory features of an outcome, such a pellet, must first become connected with a specific motivational structure; here, one sensitive to nutrient commodities (N) that is itself modulated by deprivation conditions. Activation of the nutrient center provokes activity in an appetitive affective structure (Ap), one outcome of which is an emotional response. In this view, it is the contiguous activity of the outcome representation and the emotional response that constitutes incentive learning. From this learning can be extracted more abstract values (such as good or bad—see Ref. [17] for details).

With regard to the neural bases of incentive learning (refer to Fig. 6.2B), previous findings suggest that the PL and MD are unlikely candidates for the mediation of incentive learning because they mediate goal-directed acquisition but not performance. Rather, considerable research has focused on the anterior IC and the BLA in incentive learning. The IC was first considered because of its role in gustatory (and therefore taste) processing, and the BLA was considered because of its role in regulating emotional feedback. Specifically, Balleine [17] argued that emotional responses to particular outcomes might form the bases of encoding outcome value in this manner.

In the same study in which they examined the effects of PL lesions, Balleine and Dickinson [1] investigated the effects of IC lesions using the same tasks. IC lesions, like PL lesions, were found to abolish outcome devaluation performance. However, unlike PL lesions, IC lesions left contingency degradation performance intact, suggesting that animals with IC lesions had successfully encoded the contingency between the action and the outcome. In this, and a later study [18], the authors further found that IC lesions abolished sensitivity to an incentive learning treatment that, in sham controls, reduced responding on an action paired with an outcome that they had experienced in a sated state relative to an outcome experienced while hungry. Rats with IC lesions, on the other hand, performed each action indiscriminately. Importantly, Balleine and Dickinson [18] demonstrated that this effect was confined to situations in which testing occurred in extinction, suggesting that the IC plays a role in the memory for changes in incentive value rather than in its encoding. This was later confirmed by Parkes and Balleine [19]. They demonstrated that bilateral intra-IC infusions of the NMDA receptor antagonist ifenprodil, when made after

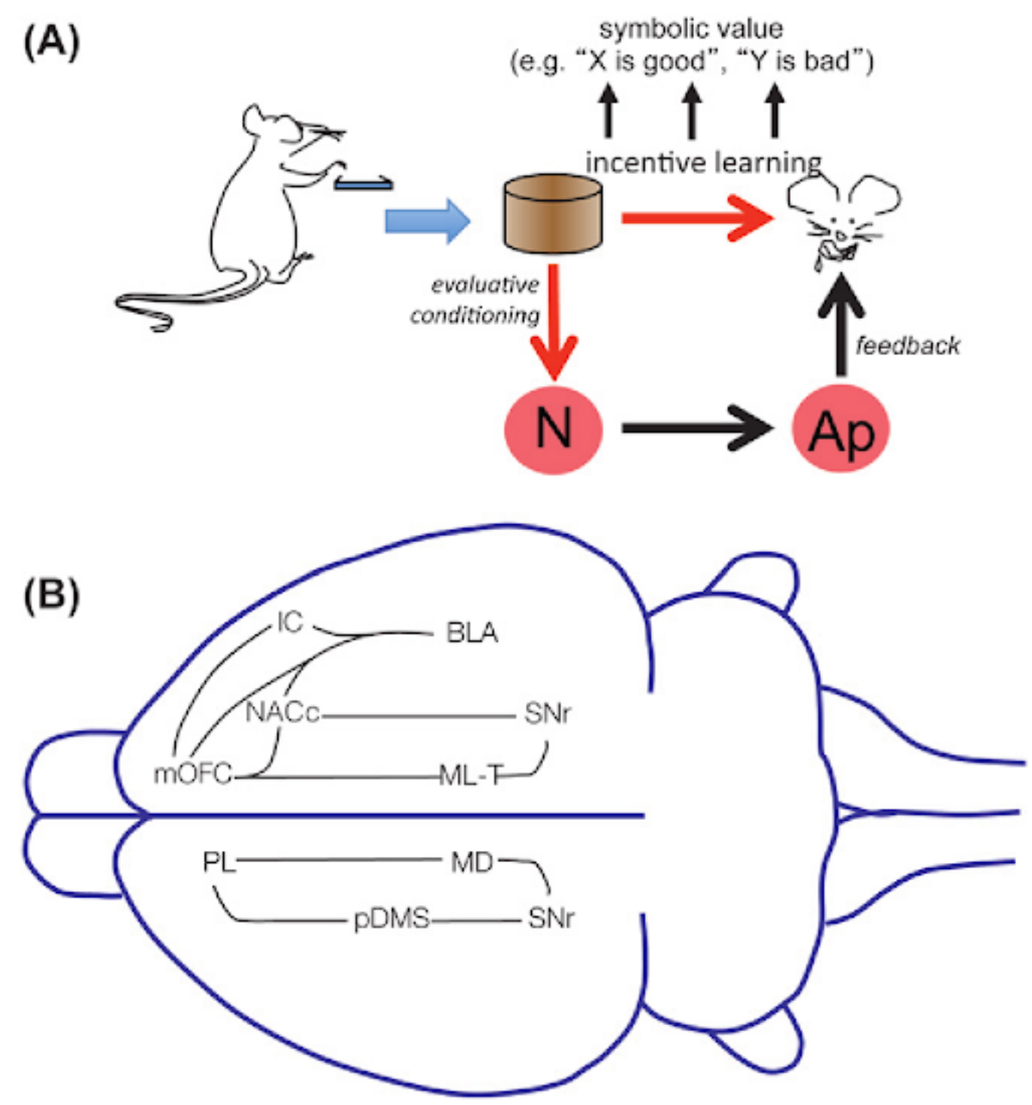

FIGURE 6.2 **Incentive learning and the neural basis of goal-directed action.** (A) Summary of the associate structure thought to underlie incentive learning. Rats learn to press a lever for an outcome, the value of which is determined by motivational and affective feedback in the form of an emotional response. The association of the sensory properties of the outcome with this emotional response constitutes incentive learning. In this example, a rat presses for a food pellet, the sensory properties of which, through evaluative conditioning, become able to activate nutrient detection processes and thus an appetitive affective center, one effect of which is the generation of a pleasant emotional response. Based on incentive learning more abstract values can be generated. (B) Summary of the neural circuits mediating incentive learning and instrumental performance (upper hemisphere) and goal-directed learning (lower hemisphere); see text for details. *N*, nutrient commodities; *Ap*, appetitive affective structure; *BLA*, basolateral amygdala; *IC*, insular cortex; *MD*, mediodorsal thalamus; *ML-T*, midline thalamus; *mOFC*, medial portion of the orbitofrontal cortex; *NACc*, nucleus accumbens core; *pDMS*, posterior dorsomedial striatum; *PL*, prelimbic cortex; *SNr*, substantia nigra pars reticulata.

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devaluation (specific satiety) but prior to a choice test, were successful in abolishing the effect of outcome devaluation on performance. Together, these experiments suggest that the role of the IC is to retrieve the incentive value of the outcome prior to test to influence performance.

So where, then, is the incentive value of the instrumental outcome encoded? Balleine et al. [20] examined whether the BLA might perform this function. First they demonstrated that lesions of the BLA attenuated outcome devaluation performance. Unlike lesions of other structures previously discussed, BLA lesions attenuated performance whether tested in extinction or in reinforced tests. A further experiment showed that these deficits were not due to BLA lesions preventing discrimination between actions (BLA-lesioned rats were able to perform these actions in a distinct sequence to achieve reward). Parkes and Balleine [19] later demonstrated that although bilateral BLA infusions of ifenprodil abolished outcome devaluation performance when administered prior to devaluation treatment (specific satiety), similar infusions given after devaluation but prior to test left performance intact. This finding, together with previous results, suggests that the BLA encodes the alteration in incentive value that occurs during sensory-specific satiety, but is not involved in the retrieval of that value. A similar result was reported by Wassum et al. [21] in an experiment in which they trained rats in a low deprivation state and reexposed them to the outcome in a food-deprived state. In that case the increase in incentive value was blocked by the infusion of the opioid antagonist naloxone into the BLA but only if the infusion was given prior to incentive learning rather than test (see Refs. [21,22], for review).

Because the BLA and the IC share strong reciprocal connections [23] Parkes and Balleine [19] hypothesized that they form a circuit in which the incentive value of the instrumental outcome is encoded by the BLA, and then retrieved by the IC, to influence performance. They developed a novel, sequential disconnection procedure to test this hypothesis. All rats received unilateral infusions of ifenprodil into the IC in one hemisphere and BLA infusions in the alternate hemisphere, but the order of infusions was altered between groups. That is, one group received the BLA infusion prior to devaluation and the IC infusion prior to testing, and the remaining group received infusions in the opposite order. It was hypothesized that if the BLA were important for encoding incentive value, and the IC important for retrieving that value, then only the group that received the BLA infusion prior to devaluation and the IC infusion prior to test should show a deficit in devaluation performance (Fig. 6.2A). This is because, first, the BLA infusion prior to devaluation treatment should block encoding of the incentive value to be retrieved by the intact ipsilateral IC on test and, second, the contralateral inactivation of the IC prior to the test should block any retrieval of incentive learning encoded by the contralateral BLA. By contrast, for the group that received the opposite arrangement, both BLAs were intact and able to encode alterations in incentive value during devaluation, and these values could be retrieved by each intact IC on testing. This was the observed result; the BLA infusion prior to devaluation and the contralateral IC infusion prior to test blocked the outcome devaluation effect, whereas the reversal of this order had no effect. This general circuit is summarized in the upper hemisphere of Fig. 6.2B.

DECIDING WHAT TO DO: THE NEURAL BASES OF OUTCOME RETRIEVAL AND CHOICE

How is information regarding the specific consequences of actions integrated with the value of those consequences so that we can choose actions appropriately? Although the IC retrieves the incentive value of a specific sensory event, when tested in extinction that value has to be linked to a specific mental representation of the instrumental outcome, including its sensory-specific characteristics. Work suggests that the integration of the retrieved value with the retrieved outcome of a specific instrumental action involves the mOFC [24]: a projection target of both the BLA and the IC [25] (see Fig. 6.2B). The mOFC also receives inputs from sensory areas, particularly olfactory regions that could carry sensory-specific information, as well as inputs from the posterior parietal cortex [25], which itself receives visual, auditory, and somatosensory information to influence planned movements. Thus, the mOFC could integrate these sensory inputs with information about available actions to retrieve the specific outcome representation to guide choice.

Our work has suggested that this role for mOFC is limited to situations in which the physical outcome is absent [24]. Specifically, we first showed that both pretraining excitotoxic lesions and posttraining mOFC inactivation by way of the hM4Di DREADDs abolished outcome devaluation performance in extinction but not reinforced tests. mOFC lesions further spared performance in paradigms in which the outcome was actually presented, such as contingency degradation. A final experiment demonstrated that animals with mOFC lesions, unlike shams, were unable to learn or be appropriately guided by specific inhibitory S−A−O contingencies, which rely on the retrieval of absent (but expected) outcomes. These findings confirmed predictions generated using simulations of reinforcement learning models in which we assumed that sham

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animals could infer "states" determined by the identity of absent outcomes, but animals with a dysfunctional mOFC could not.

The mOFC projects widely throughout the neural circuit controlling goal-directed actions, including the entire medial wall of the striatum [26]. These projections do, however, appear to be particularly strong in the ventromedial striatum, especially in the NAC core; see Chapter 1. It is of some interest, then, that this region has been specifically implicated in controlling the performance, but not learning, of goal-directed actions. Similar to IC and mOFC lesions, lesions of the NAC core have been found to abolish outcome devaluation performance but spare contingency degradation [6]. Again this suggests a role in the expression, rather than the learning, of goal-directed actions. This was confirmed by a later study [27] that found that μ opioid receptors within the NAC core underlie this effect. Specifically, bilateral intracore infusions of the μ opioid receptor antagonist D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2 (CTAP) were found to successfully abolish outcome devaluation performance. Because these infusions were administered after A—O learning and outcome devaluation had occurred, this finding suggests that the NAC core is not involved in encoding the A—O contingency or the incentive value of the instrumental outcome, but rather implies a specific role in the performance (see Refs. [21,6,28], for review); refer to Fig. 6.2B.

Like the mOFC, the NAC core also receives projections from BLA and IC. Furthermore, several studies have examined the impact of disconnecting the NAC core either from the BLA using contralateral lesions [29] or from the IC using contralateral lesions (experiment 1) or contralateral infusions (experiment 2) of the $GABA_A$ agonist muscimol into the IC and CTAP into the NAC core [30]. All of these manipulations were found to abolish the ability of animals to choose appropriately following outcome devaluation. The infusions in the latter experiment were again given after devaluation but prior to test, implicating the IC—NAC core circuit in goal-directed performance specifically.

Taken together with the findings regarding incentive learning, and as illustrated in the full circuit in the upper hemisphere in Fig. 6.2B, it appears that alterations in incentive value are encoded in the BLA and retrieved by the IC, and that this information is matched with the abstract mental representation of the outcome (including its sensory-specific characteristics) by the mOFC, which passes this information to the NAC core for the performance of goal-directed actions. Although no disconnection studies between the mOFC and any of the target structures (BLA, IC, NAC core) have yet been conducted, and thus any ideas about the functional circuitry involving the mOFC in this role are purely speculative, these studies are clearly of great potential interest particularly because they could point to a specific circuit that plays an important role in bringing A—O and reward information together to guide choice. How exactly this ventral performance circuit interacts with the learning processes supported by the dorsal striatum is another critical issue and we turn to this next.

HOW THESE CIRCUITS INTERACT: CONVERGENCE ON THE DORSOMEDIAL STRIATUM

To briefly recap, the processes controlling goal-directed actions that we have outlined here include first learning the A—O contingency, which is then integrated with the current incentive value of the outcome that has been matched with a representation of that outcome. Together these learning and reward processes are integrated to form action values, based on which distinct courses of goal-directed action can be compared. Importantly, although all of these learning and motivational processes are somewhat behaviorally and neurally separable, they are also interdependent, and we will now discuss views on how this interdependence is achieved.

As illustrated in Fig. 6.2B, a crucial circuit upon which these processes and neural inputs are likely to converge is that involving the pDMS. In rhesus monkeys, single-unit recordings from neurons in the anterior nucleus found that activity was closely correlated with the rate of instrumental learning [31] and, in humans, fMRI studies have revealed that caudate nucleus activity is modulated specifically by A—O contingency knowledge [32,33]. In rats the evidence is particularly revealing because, unlike all previously discussed structures, not only do both pre- and posttraining manipulations that inactivate the pDMS abolish outcome devaluation, they also impair contingency degradation without affecting discrimination between actions or outcomes [34,35]. Therefore, of all the structures that have been examined, the pDMS is the only one that is critical for both the learning and the expression of goal-directed actions. It appears likely, therefore, that the pDMS is the neural locus of goal-directed learning, and we will consider how each of the neural structures outlined here as important to various aspects of goal-directed action production makes contact with the pDMS.

The source of contact between the PL and the pDMS is straightforward, as there are strong ipsilateral and contralateral projections from layer 5 of the PL to the pDMS. Although there are no direct projections from the MD (the other structure specifically implicated in A—O learning) to the pDMS, the MD projects to the PL so it can influence the pDMS indirectly via that cortico-thalamic circuit. As discussed, A—O learning depends

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on the PL and MD but is not stored there: it becomes independent of the MD and PL once it is learned. It does not, however, become independent of the pDMS; therefore it is likely that A–O contingency information reaches the pDMS from the PL (and indirectly from the MD) to be stored in the pDMS. Studies in our laboratory are directly assessing these questions.

With regard to the more performance-related circuits, although a number of the studies outlined here have explored "minicircuits" (e.g., BLA–IC, BLA–NAC, and IC–NAC core), few have assessed how these circuits might make contact with the larger circuit involving the pDMS. With respect to this, it is of some interest that all of these structures, with the exception of the NAC core, project directly to the pDMS, although the relative strengths of these projections is quite varied.

In fact, of these connections, only one has been experimentally examined: that between the BLA and the pDMS [36]. For this study, each rat received a unilateral BLA lesion and a pDMS cannulation in the hemisphere that was either ipsilateral or contralateral to the lesion. They were then trained to press two levers for a common outcome (Polycose) to achieve a base rate of responding, followed by 2 days of training with specific A–O contingencies. For the 2 days that followed this initial A–O training, one group of rats received an infusion of muscimol into the pDMS just prior to being trained with the reverse of the A–O contingencies, whereas another group received an infusion of vehicle. All rats were then tested for outcome devaluation drug free. Rats that received ipsilateral muscimol infusions had encoded the reversed A–O contingencies, responding appropriately (i.e., nondevalued > devalued), whereas rats that received contralateral infusions responded according to the original A–O contingencies (devalued > nondevalued). This suggests that the infusion prevented A–O learning from occurring during reversal training without affecting initial A–O encoding. Although this finding might appear to be at odds with our previous assertion that the BLA encodes incentive value rather than A–O learning, it is clear that incentive value information provided by the BLA makes an important contribution to A–O learning during acquisition. Specifically, the prediction error signal driving selective learning (i.e., the difference between the reward that the animal predicts based on an action and that actually delivered) should be anticipated to be relatively weak in the face of a low incentive value, resulting in both a reduced asymptote and a relatively slower rate of A–O learning. As such, the rats in the experiment of Corbit et al. [36] would have strongly encoded the first set of contingencies when no infusions were given and incentive value encoding was free to influence A–O learning in the pDMS, but only weakly encoded the opposing contingencies after pDMS inactivation. Thus, when pitted against each other on the final choice test, the more strongly encoded original contingencies were those that influenced choice.

A second experiment in this series showed that outcome devaluation was abolished in animals that had unilateral BLA lesions and received contralateral pDMS infusions of muscimol prior to test, whereas it was intact in animals that received ipsilateral infusions. This is consistent with our account of BLA function because the hemisphere containing the BLA lesion could not have encoded incentive value during devaluation, and the infused pDMS in the opposite hemisphere could not retrieve any incentive value on test that was encoded by the intact BLA.

We argued that the BLA–pDMS connection mediating these effects is likely to be direct. This is partly because the major indirect pathway by which BLA-encoded information could affect A–O learning is via the PL, and PL–BLA disconnections have been found to have no impact on goal-directed learning ([37], although no attempt to sever contralateral projections was made). It is possible, however, that the BLA conveys incentive value information directly to the pDMS during A–O acquisition to influence learning, but that a wider, indirect circuit is involved in the expression of goal-directed learning during decision-making. This interpretation would fit more readily with the results of disconnection studies involving BLA and IC [19] and BLA and NAC core [29] and, indirectly, the IC and NAC core [30] examining goal-directed performance. To speculate even further, it is possible that the direct IC–pDMS and mOFC–pDMS projections also contribute to A–O learning but not performance, whereas their influence on performance is indirect, via the NAC core.

Although posttraining manipulations of IC and mOFC have been found to abolish outcome devaluation, suggesting that each of these structures plays a specific role in goal-directed performance, a possible role for these structures in A–O learning has not been explicitly ruled out (i.e., no studies have inactivated IC or mOFC during acquisition but not test). If these structures do influence A–O learning in the pDMS via direct projections, this is likely to occur via the processes that have already been identified for these structures, rather than via a direct influence over A–O learning. For example, during A–O learning the IC might mediate the continual retrieval of the incentive value of the outcomes, which would contribute to any updates in the encoding of the A–O associations. By contrast, because mOFC inactivation has been found not to influence A–O learning or responding in the presence of the outcomes themselves, mOFC–pDMS connections are likely to have little role in learning excitatory A–O associations. However, the mOFC might perform another important

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function recently identified: learning an inhibitory association between the current action and any outcomes that are not currently being presented [38]. Indeed if this type of learning proves to also depend on the pDMS, then it is likely to require inputs from the mOFC to supply the representation of the absent outcome(s).

Although highly speculative, these ideas do produce a number of testable hypotheses. For example, a direct IC−pDMS disconnection can now be achieved using a combination of wheat germ agglutinin−Cre and Cre-dependent DREADDs and should affect goal-directed learning but not performance, whereas a direct disconnection of the IC−NAC core pathway should affect performance but not learning. If correct, a final question remains with regard to how the NAC core makes contact with the pDMS to enable goal-directed responding, as there are no direct connections between these structures. One possibility that has been suggested is that it does so via the series of spiraling networks linking the striato-ventral tegmental and striatonigral pathways, which direct a "feed-forward" flow of information from the NAC core (and shell) through to the DMS (and then to the dorsolateral striatum) [39]. A second or perhaps additional alternative hypothesis is that these circuits interact in the corticothalamic pathway where they come together in the cortical basal ganglia feedback network (see Refs. [28,40], for reviews of this suggestion). Such a network has already been proposed to support the influence of reward-related cues on goal-directed action, in which integration appears to involve the corticothalamic network, particularly that linking the MD and the OFC [28]. Nevertheless, it is clear that a network centered on the MD does not support the integration necessary for changes in performance following outcome devaluation, which probably involves some other, functionally undiscovered, region of the midline thalamus (see Fig. 6.2B).

CONCLUSION

The studies reviewed here indicate that substantial progress has been made in recent years toward identifying the neural bases of the learning and motivational processes that control goal-directed actions. It is clear, however, that there is still much to be explored. With the advent of new techniques, such as DREADDs and optogenetics (see Chapter 5), as well as the diligent use of existing techniques, it is likely that many of the remaining questions will be answered in the years to come. It is further possible, even likely, that new questions will arise with the use of these new techniques, and that exploring these questions will reveal the circuits outlined here to be considerably more complex than currently characterized. Indeed, there are several layers of complexity that we are already aware of but that are beyond the scope of this chapter. For example, we have focused entirely on the circuits that underlie self-initiated goal-directed actions and ignored the rich literature examining the neural circuitry underlying goal-directed actions that are elicited by Pavlovian stimuli (i.e., Pavlovian−instrumental−transfer). Furthermore, we have not explored evidence demonstrating that parafascicular thalamic-controlled cholinergic interneurons in the pDMS control learning about any alterations in already-learned A−O contingencies but leave original contingencies unaffected [41]. Nevertheless, a great deal has been already achieved in the process of delineating these circuits, and it will be of significant interest to continue to add to this rapidly developing literature.

Acknowledgments

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CHAPTER

7

Impulsivity, Risky Choice, and Impulse Control Disorders: Animal Models

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Abstract

The neural and neurochemical bases of various forms of impulsive behavior in rodents are reviewed. We distinguish three main forms of impulsivity: waiting impulsivity (based on premature responding in the five-choice serial reaction time task and delayed temporal discounting of reward), risky choice impulsivity (based on probabilistic discounting of reward), and stopping impulsivity (based on stop-signal inhibition). Some of these forms have trait-like characteristics. Dopamine- and serotonin-dependent functions of the nucleus accumbens are implicated in waiting impulsivity and risky choice impulsivity, as well as cortical structures projecting to the nucleus accumbens. For stopping impulsivity, dopamine-dependent functions of the dorsal striatum are implicated, as well as circuitry including the orbitofrontal cortex and dorsal prelimbic cortex. The noradrenaline reuptake blocker atomoxetine ameliorates both waiting impulsivity (reducing premature responding and enhancing tolerance to delayed gratification) and stopping impulsivity (speeding the stop-signal reaction time), effects that are mediated in the shell region and the prefrontal cortex, respectively. Differences between the contrasting forms of impulsive responding, as well as their commonalities, are highlighted, suggesting that impulsivity is not a unitary construct. Various applications to human neuropsychiatric disorders such as drug addiction and attention deficit/hyperactivity disorder are discussed.

Impulsivity, the tendency to respond prematurely or in an unduly risky fashion, is becoming an increasingly important construct in psychiatry. The emphasis in this working definition of impulsivity is on its potentially maladaptive nature; clearly there are occasions when it is advantageous to respond quickly and in a risky manner. Thus, impulsivity is a dimensional construct that can describe not only behavior of the healthy population, but also a range of psychiatric symptoms expressed in disorders as seemingly distinct as drug addiction, attention deficit/hyperactivity disorder (ADHD), obsessive–compulsive disorder, mania, schizophrenia, and Parkinson's disease. From that perspective "impulsivity" may qualify for what has been described by the National Institute of Mental Health as a research domain criterion [1], cutting across traditional psychiatric categories. For this to be the case, impulsivity would also have to be tied to specific neurobehavioral processes, possibly also linked to genetic factors. There is every indication that impulsivity meets these requirements. Thus, the aforementioned definition also captures the fact that there is emphasis on anticipating goals or outcomes—at the beginning of response sequences prior to response initiation, when it is important, not only to select responses appropriately, but also to perform the response at the right time and place. Such processes have now been linked definitively to the functions of neural networks of the basal ganglia, including the nucleus accumbens and its contributions to reward-related, goal-directed responding. We have previously referred to this form of impulsive behavior as "waiting impulsivity" [2].

In clinical applications, impulsivity is often measured in terms of self-report, as in the Barratt Impulsiveness Scale (BIS) [3], which contains questions about everyday behavior such as whether individuals make comments "without thinking" and whether they switch jobs frequently or feel "restless in lectures." While such questionnaires are useful and sensitive clinical instruments, they are subjective and often do not reflect what is measured more objectively by other methods. In fact, measures of impulsive behavior frequently do not intercorrelate very highly, suggesting that impulsivity is not a unitary construct, a theme we will develop further later. However, the availability of several objective measures of impulsive responding that can be used across species has been an advantage for establishing the neural

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networks of various forms of impulsivity. In this chapter we will refer to several methods for measuring impulsive behavior, ranging from temporal and probabilistic discounting of reward to measures of "motor impulsivity" such as go/no-go performance, premature responding in the five-choice serial reaction time task (5CSRTT), and also differential reinforcement of low rates of responding (DRL schedules). We will also consider the stop-signal reaction time as another prominent example of requirement of response inhibition when the response has already been initiated. After an initial survey of these procedures, we will discuss how they have been used to define the involvement of discrete neural circuitries in control of impulsive behavior (Fig. 7.1).

DELAYED AND PROBABILISTIC DISCOUNTING: "IMPULSIVE CHOICE" IN DECISION-MAKING

Delayed gratification, or impulsive choice, procedures have been developed in animals including pigeons as well as rodents, but are also applicable to humans. Much early work [4–6] showed that individuals (pigeons, rats, or humans) have distinct discounting functions, hyperbolic in form, with regard to delay, magnitude, and probability of reinforcement, and that certain patient groups, notably drug abusers, discount at significantly steeper rates than healthy volunteers, in other words, exhibiting impulsive choice. Perry and Carroll [7] provide an excellent review of the relevance

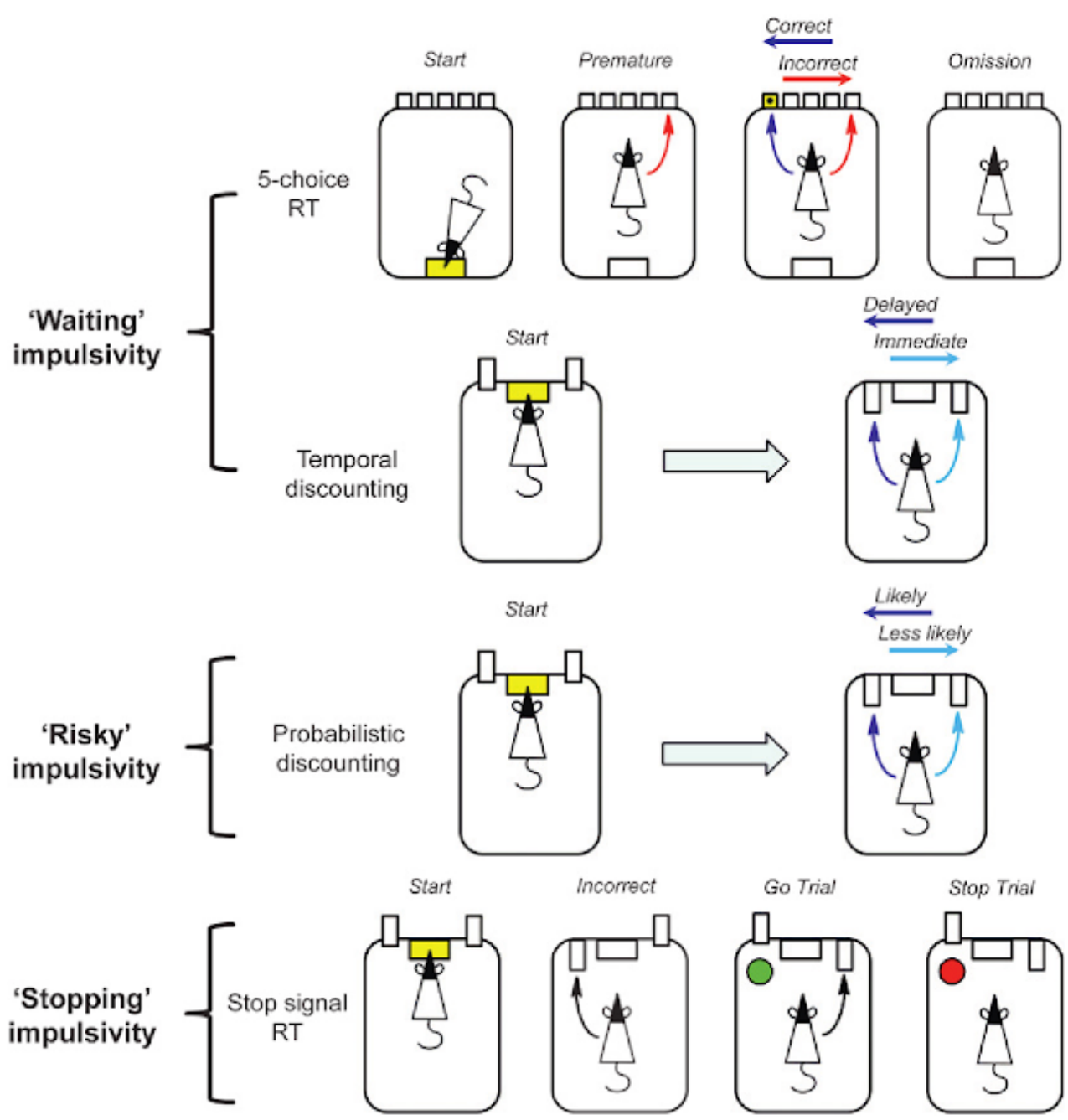

FIGURE 7.1 Translatable subtypes of impulsivity and their operational assessment in rodents. The schematic depicts the multifaceted nature of impulsivity and its hypothetical component dimensions of waiting, risk-taking, and stopping. "Waiting" impulsivity is assessed by the inadequate suppression of responses made prepotent by their association with reward, leading to a "premature" response on the five-choice serial reaction time task (or the analogous four-choice task in humans), and by a preference for instant, small-magnitude rewards, assessed by temporal discounting procedures. "Risky" impulsivity refers to the tendency to prefer less certain, large-magnitude rewards over smaller, but more certain rewards. "Stopping" impulsivity is widely assessed by stop-signal reaction time procedures in rodents and humans, a form of motor impulsivity requiring inhibition after, rather than before, response initiation. *RT*, reaction time.

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of this form of impulsivity to drug abuse. Evenden [8] was perhaps the first to consider temporal discounting in comparison to other models of impulsivity. Cardinal [9] has reviewed, in considerable detail, the neural and neurochemical basis of behavior under delayed and probabilistic reinforcement; this review serves to update and extend that previous synthesis, for reasons of space.

In temporal discounting procedures, a choice is generally given between a small immediate reward and a delayed larger one. In this case, impulsive choice is reflected as a preference for the smaller, more immediate outcome. The resulting behavior can usually be modeled as a hyperbolic function in which the constant k can provide an index of temporal reward discounting and hence also of impulsive choice [4,5]. A parallel case is that of "probability discounting," in which the same general principles obtain, but in which the risky aspects of impulsive behavior are measured as preference for the larger, but less likely, option. This paradigm is best suited to human studies of decision-making under risk and is directly relevant to such paradigms as the Iowa Gambling Task [10] and the Cambridge Gambling Task [11]. Temporal and probabilistic discounting clearly overlap and engage similar processes in theoretical terms [12]; however, there is mounting evidence that they are in fact distinct and both contribute to complex decision-making processes [9].

There are further, major methodological problems for delayed discounting both for human and for experimental animal paradigms. Human temporal discounting of reward is generally measured by giving subjects hypothetical choices; for example, the possibility of receiving £X now and £Y after some elapsed time, often large numbers of days. Hence, actual behavior is not measured and one cannot be absolutely sure that people will actually do in practice what they say they will do in the abstract. The problem with the animal paradigms of temporal discounting is somewhat different; one has to be sure that the animal is able to bridge delays of many seconds between its response and an outcome; in other words to learn with delay of reinforcement, for which most species have severely limited capability. One way of ameliorating this difficulty is to provide an immediate conditioned reinforcer that is associated with the eventual large reward outcome.

Temporal and probabilistic discounting are clearly important potential components of decision-making under risk and uncertainty. However, also important is the capacity to accumulate relevant information to a point at which a decision can be made with confidence. The tendency to choose too soon under conditions when insufficient evidence has accumulated may be referred to as "reflection impulsivity." This is an important construct in developmental psychology, but has recently been employed in studies of adults. Animal tests of reflection impulsivity are certainly feasible but have not so far been widely employed [8].

PREMATURE RESPONDING IN THE 5CSRTT

The discovery that individual differences in the premature responding of rodents in the attentional setting of the 5CSRTT [13] is associated with an increased propensity for cocaine, nicotine, and sucrose reinforcement [14–16] has led to considerable interest in the nature of this potential behavioral endophenotype. In the 5CSRTT, rats or mice are trained to detect brief visual stimuli to earn food reinforcers by a nosepoke response in the illuminated location. Incorrect or premature nosepoke responses are punished by a time-out from reinforcement, signaled by dimming of the house lights. Individuals vary considerably in their tendency to respond prematurely, although the persistence of this tendency makes it a likely trait measure of impulsivity. The 5CSRTT essentially incorporates a DRL contingency in its design, and so it is likely that efficiency of performance in DRL schedules also reflects a tendency toward premature responding, although the typically longer intervals for which responding has to be inhibited make timing an even more important requirement than in the 5CSRTT. There are also elements of the requirement for go/no-go choice responding in the 5CSRTT, but this is clearly a distinct requirement, at the point of response selection.

The 5CSRTT is in fact based on a human analogue of the task, previously much used for examining effects of stressors, fatigue, and drugs on human performance, including sustained attention [13]. In 2013, the rodent 5CSRTT was adapted for a human version with four choices (4CSRTT), which lays emphasis on measuring premature responding as premature release of a response button prior to touching a screen at the location of a briefly presented visual target [17].

STOP-SIGNAL REACTION TIME

The stop-signal reaction time (SSRT) task is well established as a paradigm for measuring response inhibition and volitional control in humans [18]. Impairments in response inhibition are associated with impulsivity. However, the key point of the SSRT task, which distinguishes it from other measures of motor impulsivity, is that inhibition is applied after, rather than prior to, response initiation. Thus, we have previously distinguished "waiting impulsivity" from that exemplified in SSRT performance as "stopping

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impulsivity" [3]. Other than being more relevant following rather than prior to response initiation, "stopping inhibition" can be distinguished from "waiting inhibition" in terms of the underlying neural networks engaged by each task. Effective translation of the SSRT paradigm has been achieved in nonhuman primates, rats, and mice (eg, [19]), with often striking similarities in typical values of key variables such as SSRT that encourage the conclusion that similar processes are being engaged in animal and human studies.

NEURAL BASIS OF IMPULSIVITY

This review focuses on evidence gained from animal models of impulsivity, but the similarity of some of the procedures employed is useful for cross-species comparative studies of their neural substrates and homologies, using, for example, brain imaging methodology for humans. In general, it appears that corticostriatal pathways are especially implicated in various forms of impulsivity, although with considerable overlap of some key structures. An especially important consideration is the parallel nature of the corticostriatal parallel "loop" pathways, which are fed back via pallidal and thalamic nodes to the frontal cortex; waiting and stopping impulsivity appear, for example, to utilize distinct, though parallel, systems [3]. Moreover, choice and motor aspects of waiting impulsivity, while converging in the nucleus accumbens, also appear to utilize different systems. Finally, the different forms of impulsivity may be subject to distinct modes of chemical neuromodulation by the ascending monoaminergic systems, which may have implications for the treatment of such conditions as ADHD.

NEURAL SUBSTRATES OF WAITING IMPULSIVITY

5CSRTT Premature Responding

Premature responding on the 5CSRTT clearly depends on dopamine (DA)-dependent mechanisms in the nucleus accumbens. Initial evidence showed that the tendency of D-amphetamine to induce premature responding, whether the drug was infused systemically or centrally, depended on the integrity of the DA innervation of the nucleus accumbens [20]. Moreover, this premature responding could be blocked by infusions of intraaccumbens DA receptor antagonists such as the mixed D1/D2 antagonist α-flupenthixol and also the D1 receptor antagonist SCH22390 or the D2 receptor antagonist sulpiride. The nucleus accumbens is divided into two subregions, the shell and the core, but both are implicated in this behavior. Effects of excitotoxic lesions of the nucleus accumbens on baseline premature responding have been quite inconsistent. Christakou et al. [21] found that lesions of the core region mainly increased premature responding following an error on the previous trial, suggesting that the arousal induced by frustrative nonreward may contribute to premature responding. This evidence of core involvement is further substantiated by effects of core lesions on responding under DRL schedules, which typically require inhibition of responding for periods of up to 18 s [22].

Murphy et al. [23] showed that core lesions exacerbated the effects of systemic D-amphetamine to elevate premature responding, whereas lesions of the shell actually reduced such responding following D-amphetamine. This evidence suggested a form of opponency in the control over responding by the core and shell subregions; further evidence in support of this opponency comes from the contrasting effects of deep brain stimulation on impulsivity [24] and divergent changes in electrically evoked DA release in these two regions in low- and high-impulsive rats [15].

Other evidence has shown that damage to the infralimbic (IL) cortex, anterior cingulate, and hippocampus can all enhance premature responding in the 5CSRTT, suggestive of top-down inhibitory influences [3]; these structures project to the shell (especially hippocampus and IL cortex) and the core accumbens subregions. It should also be noted that damage to the dorsomedial striatum can also enhance premature responding but often in the context of more general changes in performance [3].

Studies of individual differences in impulsive responding on the 5CSRTT have greatly bolstered these conclusions. Dalley et al. [25] originally noted that the large, though consistent, individual variation in premature responding to a single, fixed location was suggestive of impulsive trait. Studies (Dalley et al., unpublished findings) have shown that the 5CSRTT impulsivity indeed breeds true over four generations and is heritable, with a quantitative trait locus on chromosome 1 that includes genes for synaptic proteins and the GABA and mGluR5 receptors. The phenotype was quite specific; the high-impulsive rats were not overactive or disposed to stress reactions, nor did they exhibit impaired Pavlovian or instrumental learning. They did show a mild novelty preference and occasionally a mild attentional impairment [3].

Subsequent to screening, high-impulsive rats were also shown, however, to exhibit elevated self-administration of cocaine in a binge access paradigm [14]. Other studies reported similarly enhanced nicotine [15], but not opiate, self-administration [3]. The elevated cocaine self-administration occurred in high-impulsive rats even if punished with electric shock [26] and so

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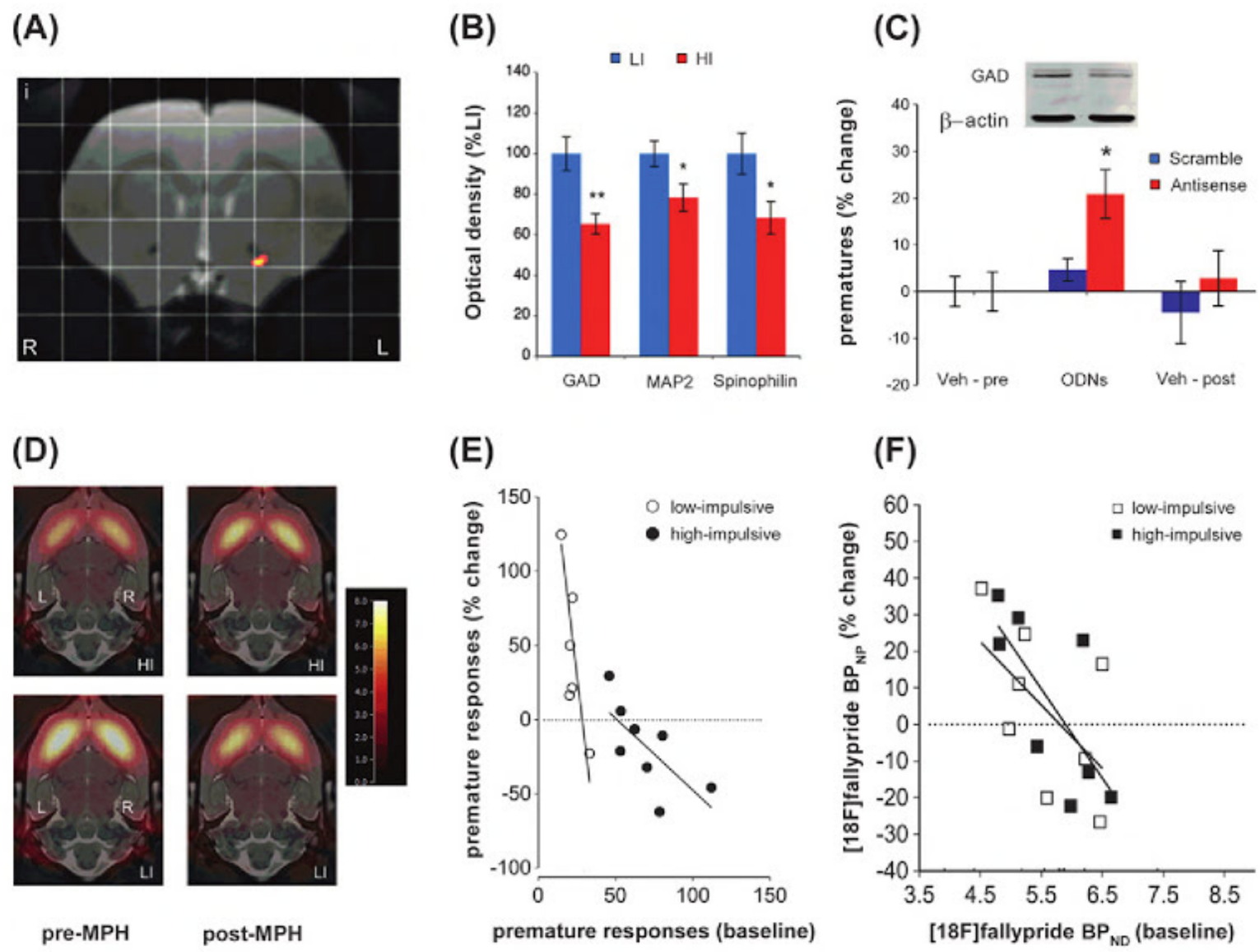

FIGURE 7.2 Neural mechanisms underlying trait-like impulsivity in rats. (A) In vivo magnetic resonance (MR) scan image showing reduced gray matter density in the left nucleus accumbens core of low- versus high-impulsive rats *(LI, HI)* on the five-choice serial reaction time task. (B) Reduced levels of glutamate decarboxylase *(GAD)*, the rate-limiting enzyme for GABA, and markers of dendritic spines [microtubule-associated protein-2 *(MAP2)*, spinophilin] in the left nucleus accumbens core of high-impulsive rats. (C) Increased impulsivity in low-impulsive rats following transient inactivation of GAD in the nucleus accumbens core by locally administered antisense oligonucleotides *(ODNs)*. (D) Coregistered MR structural scans (gray scale) and positron emission scans showing uptake of the selective, high-affinity D2/3 receptor antagonist [^{18}F]fallypride in the ventral striatum of low- versus high-impulsive rats prior to, and after, oral methylphenidate *(MPH)* administration. MPH increased uptake when baseline [^{18}F]fallypride binding was low, as in HI rats, but decreased binding when baseline binding was high, as in LI rats. (E) Rate-dependent effect of MPH on behavioral impulsivity. MPH had the effect of reducing impulsivity when baseline impulsivity was high (HI rats) but increased impulsivity when baseline impulsivity was low (LI rats). (F) Baseline-dependent effects of MPH on D2/3 receptors in the ventral striatum of LI and HI rats. MPH increased [^{18}F]fallypride uptake when baseline binding was low but had the opposite effect when baseline binding was high. *Veh*, vehicle; BP_{ND}, nondisplaceable binding potential. *Reproduced with permission from Caprioli D, Sawiak SJ, Merlo E, Theobald DE, Spoelder M, Jupp B, et al. Gamma aminobutyric acidergic and neuronal structural markers in the nucleus accumbens core underlie trait-like impulsive behavior. Biol Psychiatry 2014;75:115–23. and Caprioli D, Jupp B, Hong YT, Sawiak SJ, Ferrari V, Wharton L, et al. Dissociable rate-dependent effects of oral methylphenidate on impulsivity and D2/3 receptor availability in the striatum. J Neurosci. 2015;35:3747–55.*

could be described as compulsive—an important sign of drug addiction as distinct from recreational drug use. Of considerable significance was that D2/3 receptor binding was reduced in the ventral (nucleus accumbens) but not dorsal striatum of high-impulsive rats before they were exposed to cocaine, suggesting that low D2/3 binding was an endophenotype for stimulant abuse and relevant to the interpretation of analogous findings of Volkow et al. [27] of reduced D2/3 binding potentials in the dorsal striatum of drug abusers.

These findings were substantiated by several studies. Besson et al. [28] showed that mRNA for D2 receptors was reduced specifically in the shell region. Jupp et al. [29] used autoradiographic methods to show similarly that there was reduced D2/3 receptor protein expression in the shell, but not the core, accumbens subregions. This was accompanied by evidence of reduced DA transporter binding in the shell and D1 receptor binding in the core region. Besson et al. [30] found that infusions of the D3/D2 antagonist nafodotride into the shell region increased premature responding, whereas infusions into the core region actually reduced such responding, again demonstrating apparent opponent actions of core and shell in the regulation of behavior. Together with evidence of increased DA release in the shell region [15], these findings point to elevated DA release in the shell region being associated with high impulsivity. Thus, low presynaptic levels of D2/3 receptors in the shell region will tend to enhance DA release and high extracellular levels would be sustained by the reduction in DA transporters, which would normally regulate such excessive overflow. So far, in vivo dialysis measures of accumbens DA have not revealed direct evidence of elevated levels of DA, but this failure

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may be a product of low temporal resolution and a failure to distinguish phasic DA release.

The involvement of the core subregion has been confirmed by a 2014 study in which magnetic resonance imaging was used to show a reduced signal in the core subregion of high-impulsive rats that correlated to a very high extent in the left core subregion with levels of impulsive responding [31]. Associated with this finding was reduced activity of GABA decarboxylase (GAD) in the left core (and not the shell) subregion of high-impulsive rats, as well as evidence of a reduction of synaptic proteins. The reduced GAD activity presumably reflects reductions in numbers of medium spiny output neurons or the density of dendritic spines in the core region. The causal role of the core subregion was shown by the effects of GAD antisense infused into that region in low-impulsive rats, which selectively increased levels of premature responding [31] (Fig. 7.2).

Therefore, it would appear that the shell and core subregions interact to some extent in the production of this form of impulsivity: elevated DA in the shell presumably enhances output of this structure, which is normally counteracted or gated by core output, but less effectively so in the high-impulsive rats.

An early observation was that cocaine intravenous (IV) self-administration appeared to reduce high levels of premature responding [14], raising the possibility that this impulsivity was regulated by drugs with similar actions on catecholamine transporters, such as methylphenidate, which are used in the treatment of ADHD. This modulation has been studied in much more detail. Caprioli et al. [32,33] have examined the effects of IV self-administered cocaine and also systemic methylphenidate on impulsive responding and striatal D2/3 receptor binding. These authors replicated the finding of diminished D2/3 receptors in the nucleus accumbens associated with high levels of impulsive responding, although this was shown only for the left hemisphere. Both IV cocaine and oral methylphenidate given subchronically reduced impulsivity in high-impulsive rats, whereas it increased in animals with low levels of impulsivity—a variation of the well-known rate dependency effect. Parallel effects were observed for D2/3 binding. Thus, for example, previously low levels of striatal D2/3 binding were increased by cocaine but previously high levels (associated with high impulsivity) were decreased. However, unlike the effects for behavioral impulsivity, these effects were found for both the ventral and the dorsal striatum. Moreover, these receptor changes were found not to covary predictably with behavioral changes, suggesting that other factors may be operating to reduce impulsivity. Nevertheless, it appears that blocking the reuptake of DA can have the apparently paradoxical effect of reducing impulsivity associated with increased DA release. An explanation of this, as well as other rate-dependent effects, is required, but may reflect an altered functional balance between tonic DA levels and phasic DA neuronal activity [34].

An obvious additional candidate for modulating impulsive responding is central noradrenaline (NA), as the NA transporter is also a target for methylphenidate and cocaine. In fact, the NA reuptake blocker atomoxetine is a very effective antiimpulsivity agent, reducing impulsivity at doses that do not affect attentional performance [35]. Remarkably, when infused into the shell [but not the core or the prefrontal cortex (PFC)] region it also dose-dependently reduces impulsive responding [36]. Presumably, the drug interacts with the sparse noradrenergic innervation of the basal ganglia, which is most pronounced for the shell region [37].

In addition to regulation by DA and NA, impulsivity is also modulated importantly by serotonin (5-HT) mechanisms. Infusion of 5-HT2A receptor antagonists (ketanserin or M100907) or a 5-HT1A agonist (8-OH-DPAT) into the medial PFC reduces impulsivity, perhaps via the IL−PFC pathway [38]. These effects are mimicked by infusion of M100907 directly into the nucleus accumbens. Moreover, impulsivity is enhanced by infusions of the 5-HT2C antagonist SB-242084 into the nucleus accumbens [39]. This is consistent with earlier evidence that profound forebrain depletion of 5-HT by infusions of the selective neurotoxin 5,7-dihydroxytryptamine also led to enhanced impulsive responding [40,41], which was further exacerbated by systemic treatment with SB-242084.

Mouse models have also augmented our understanding of impulsive responding in the 5CSRTT. Mice are capable of excellent performance in this task and a large number of genetic strains have now been studied in particular with respect to the premature response measure [42]. One particular finding of interest has been that the deletion of the gene controlling α-synuclein decreases impulsivity in mice [43].

In summary, premature responding in the 5CSRTT is governed by a network of brain regions including the PFC and nucleus accumbens (core and shell) and is prevalent in disorders including ADHD and drug addiction. While we have begun to construct a neural network for the mediation and modulation of this behavior, little is known of the relationship between neural activity in these regions [44]. Therefore, we investigated local field potential (LFP) oscillations in distinct subregions of the PFC and nucleus accumbens during performance of the 5CSRTT. The main findings showed that the power in γ frequency (50−60 Hz) LFP oscillations transiently increased in the PFC and nucleus accumbens both during the anticipation of a cue signaling the spatial location

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of a nosepoke response and, again, following correct responses, confirming our hypothesis that this form of impulsivity was related to reward anticipation [45]. γ oscillations were coupled to low-frequency δ oscillations in both regions; this coupling strengthened specifically when an error response was made. θ (7–9 Hz) LFP power in the PFC and nucleus accumbens increased during the waiting period and was also related to response outcome. Additionally, both γ and θ power were significantly affected by upcoming premature responses as rats waited for the visual cue to respond. In high-impulsive rats we found that impulsivity was associated with increased error signals following a nosepoke response, as well as reduced signals of previous trial outcome during the waiting period [45]. This evidence is consistent with the previous findings that high impulsivity often follows errors or activation produced by excessive DA release, as occurs following treatment with psychomotor-stimulant drugs.

Other sources of evidence tend to support our view of waiting impulsivity as exemplified by premature responding on the 5CSRTT. Human studies of impulsivity are consistent with low D2/3 binding in the midbrain predicting impulsivity as measured by the BIS; this would also lead to elevated DA release in terminal domains in the ventral striatum [46]. There has as of this writing been little parallel evidence in humans; however, the 4CSRTT described earlier has identified elevated premature responding in methamphetamine and recreational cannabis abusers [17]. Moreover, tryptophan depletion (which transiently reduces central 5-HT) significantly increased premature responding in human volunteers [47], analogous to the effects of forebrain 5-HT depletion in rats [40]. Further evidence for a role of the nucleus accumbens in impulsivity comes from converging evidence of other forms of waiting impulsivity, notably delayed discounting of reward.

Temporal Discounting of Reward

Nucleus Accumbens

Cardinal et al. [48] initially reported that selective bilateral excitotoxic lesions of the nucleus accumbens core region (but not the anterior cingulate or the medial PFC) resulted in more impulsive choice using a temporal discounting task. In general, this result has held up in subsequent studies using different variants of the delayed discounting procedure. Thus, Pothuizen et al. [22] also varied the uncertainty of reward and showed at certain parameters that core lesions similarly enhanced choice for the immediate outcome. Bezzina et al. [49] reported a selective reduction of the intercept of an indifference function in core-lesioned rats, which indicates a higher rate of delay discounting. One issue of interpretation is whether these effects are confounded by effects on discrimination of magnitude of reinforcement [50] or on the memory for a response following delay of reinforcement [51]. However, Bezzina et al. [49] concluded that effects on reinforcement discrimination, while present, were insufficient to account for impulsive choice following core lesions. Moreover, da Costa Araujo et al. [52] concluded that the effects on delay of reinforcement were similarly insufficient to account for changes in discounting.

Delays in discounting tasks can be signaled by feedback stimuli following choice of the delayed outcome and apparently have an important influence on effects of drugs and lesions. Cardinal et al. [53] showed that D-amphetamine promoted choice for the larger, delayed reinforcer in the presence of the signaled delay, but impulsive choice in its absence, possibly consistent with other evidence that D-amphetamine enhances effects of conditioned reinforcers in their control over behavior [54]. As D-amphetamine is an indirect DA agonist, the potentiation of conditioned reinforcement through a DA-dependent mechanism in the nucleus accumbens is intuitively attractive, as its actions on temporal discounting are similarly mediated by this region. However, it appears that the situation may be more complex and depends on an interaction of DA and 5-HT mechanisms in the mesolimbic system [55].

Winstanley et al. [56] found, after extensive training in a delayed discounting procedure, that there was considerable variation in the extent of impulsive choice across a group of rats. Those rats that exhibited impulsive choice (ie, low k values) preferred the large delayed reinforcer to a greater extent after systemic D-amphetamine and this effect was reduced both by forebrain 5-HT depletion and by α-flupenthixol, the mixed D1/D2 receptor antagonist. In a later study [57], the 5-HT1A receptor agonist, 8-OH-DPAT, also antagonized the effects of D-amphetamine to reduce impulsive choice, whereas the 5-HT1A antagonist WAY 100635 potentiated it, presumably acting at 5-HT-inhibitory autoreceptors. Acute 8-OH-DPAT increased impulsive choice, an effect that depended on the integrity of the DA innervation of the nucleus accumbens [57]. This finding is consistent with the evidence that, at least under certain parameters, central 5-HT depletion can cause steep temporal discounting of reward [58]. Additionally, in vivo microdialysis has been used to measure DA and 5-HT changes selective to temporal discounting with appropriate yoked controls for the contribution of contingency. Findings indicated some selective changes in 3,4-dihydroxyphenylacetic acid, a primary DA metabolite, in the orbitofrontal cortex (OFC) and 5-HT in the medial PFC. In short, temporal discounting is powerfully modulated by both dopaminergic and serotoninergic influences, within the nucleus accumbens and various sectors of the PFC [59].

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Amygdala and Corticolimbic Influences

Winstanley et al. [60] showed that rats with excitotoxic lesions of the basolateral nucleus of the amygdala exhibited a form of impulsive choice that was similar to that following lesions of the nucleus accumbens core, perhaps reflecting the innervation of this structure. Similar effects of hippocampal lesions on impulsive choice were also reported by Cardinal and Cheung [61].

By contrast, Winstanley et al. [60] also showed that similar, large lesions of the OFC produced a paradoxical preference for delayed food rewards. The fact that the delay did not devalue the large reward to such an extent in OFC-lesioned animals supported the suggestion by Schoenbaum et al. [62] that the OFC is involved in updating the incentive value of outcomes in response to devaluation. The effects of these OFC lesions thus contrasted with the lack of effect shown of lesions of the anterior cingulate or medial PFC previously reported by Cardinal et al. [48]. They also contrasted with the findings of a notable previous study by Mobini et al. [63] in which OFC lesions made prior to the acquisition of the delay-discounting choice procedure had had precisely the opposite effect: to increase impulsive choice. At the time of that publication, Winstanley et al. [60] explained the anomaly by citing evidence that the ability of OFC neurons to encode the expected value of reward occurred only relatively late in training. The tasks used also differed in that Mobini et al. [63] offered rats a choice between a one-pellet immediate and a two-pellet delayed reinforcer, whereas Winstanley et al. [60] gave them the option of a one-pellet immediate versus a four-pellet delayed reinforcer. Thus, an increase in reward magnitude discounting following OFC lesions could possibly mask any changes in delay discounting. For example, if small rewards are also delayed, this greatly increases preference for the large delayed reward. In fact, Kheramin et al. [64,65] had shown that OFC lesions and OFC DA depletion both appear to increase sensitivity to (or discounting of) both delay and magnitude of reward.

However, a later study, using a T-maze procedure to investigate impulsive choice, also found that OFC lesions produced impulsive choice in previously trained rats [66], providing another contrast with the findings of Winstanley et al. [60], and so it is clear that it is necessary to consider other possible variables to explain these apparent discrepancies. One such variable, which may have influenced the effects of OFC lesions in all of these studies, and, as described earlier [53], has been shown to modulate the effects of amphetamine, is the presence of a cue bridging the delay between response and large reinforcing outcome. Zeeb et al. [67] found that when the delay to the large reward was cued, transient inactivation of the OFC (using a baclofen/muscimol mixture) increased impulsive choice in rats with low baseline levels of impulsivity. In contrast, the same treatment decreased impulsive choice in the uncued condition in highly impulsive animals. The effects of the cue were also found to be D2 receptor dependent, as intra-OFC infusion of a D2 receptor antagonist blocked its ameliorative effects on impulsive choice. Thus, when baseline levels of impulsive choice are high, as often occurs in rats with uncued delays, OFC lesions tend to reduce impulsive choice, as may have occurred in the Winstanley et al. [60] study. By contrast, when the large delayed reward is cued, as occurred in Mobini et al. [63] and may well have occurred in the T-maze study of Rudebeck et al. [66], inactivation of the OFC leads to impulsive choice.

Yet another factor influencing the outcome of these studies of OFC manipulations on impulsive choice is the precise site of the lesion or inactivation. All of the interventions within the OFC in the previous studies described above have centered on the ventrolateral OFC region to varying extents. However, in their study of delayed discounting, Mar et al. [68] explicitly employed discrete excitotoxic lesions of the medial OFC and ventrolateral OFC, as well as larger lesions including both structures. Ventrolateral OFC lesions induced stable patterns of impulsive choice, whereas medial OFC lesions after retraining had opposite effects. Entire OFC lesions initially replicated the effects of Winstanley et al. [60], but were transient, perhaps consistent with the interactive but opponent sequelae of the two component regions. These differential effects presumably reflect the possible role of the lateral OFC in cognitive control processes when reward-related responses require suppression, a hypothesis supported by the slowed reversal learning of lateral OFC-lesioned rats when the location of the reward contingencies was switched. By contrast, medial OFC-lesioned rats after retraining appear to be more sensitive to reward magnitude, which counteracts delay devaluation, similar to the effects of larger lesions in Kheramin et al. [63].

Overall, these findings are probably relevant to human findings for hypothetical temporal reward discounting, but there are apparent discrepancies. The increased impulsive choice following lateral OFC lesions in rats may be consistent with evidence in humans that the degree of activation during reward discounting of lateral OFC predicts the extent of deferral of gratification [69]. However, less consistent is the finding that humans showed impulsive choice in three separate paradigms following medial OFC damage [70].

The McClure et al. [69] functional imaging study in humans varied both delay and magnitude for reward and found evidence for two interactive systems of choice, an interaction of which may explain hyperbolic

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discounting. These systems consist of a "declarative, rational discounting" component including parietal and lateral OFC areas and a system more sensitive to immediate effects of highly salient rewards, focused on the medial OFC and nucleus accumbens. However, the effects of nucleus accumben regions to enhance impulsive choice reviewed earlier (eg, [48]) appear to be inconsistent with this formulation, possibly depending on the differences between hypothetical and actual reward discounting.

NEURAL SUBSTRATES OF PROBABILITY DISCOUNTING OF REWARD: RISKY CHOICE

Risky choice is that between more certain small rewards and less certain large rewards. Although probability discounting can be subsumed in the same theoretical framework as temporal discounting [12], it appears that the underlying neural substrates are distinct. Correlational studies in humans are consistent with evidence that the nucleus accumbens might also be implicated in probabilistic discounting in animals. Thus, for example, midbrain DA neurons innervating the nucleus accumbens fire in relation to reward probability in monkeys [71] and an increase in blood flow occurs in the human nucleus accumbens just prior to risk-taking decisions in human volunteers [72]. Moreover, lesions of the nucleus accumbens core [73] and lateral OFC [63] induce risk-averse choice in rats. Effects of inactivation of the nucleus accumbens with acute infusions of GABA agonists were broadly similar but distinct contributions of the shell and core subregions were obtained [74]. Manipulation of DA receptors in the nucleus accumbens has complex results; D1 receptor blockade reduces risky choice, much like lesions or inactivation; a D1 receptor agonist appears to optimize risky choice. D3 receptor antagonism has effects almost opposite to those of D1 receptor antagonism; surprisingly D2 receptors play no obvious role [75]. A parallel analysis of effects of DA receptor agents in the rat medial PFC showed that, again, D1 receptor blockade reduced risky choice, whereas D2 receptor blockade had the opposite effect [76]. These findings are consonant with the relationship of tonic fluctuations of DA release to several factors influencing risky choice in the nucleus accumbens, and contrast with the more obvious "reward metering" provided by DA release in the PFC, somewhat independent of precise contingencies [59,77]. These are striking results, as one would normally associate impulsivity with risk-taking as well as temporal discounting of reward; it suggests either that our notions of impulsivity have to be revised or that these structures are associated only with certain forms of impulsivity.

Following up the findings of dissociable effects of manipulations of medial OFC lesions on temporal discounting [68], Stopper et al. [78] investigated the contribution of the rat medial OFC to risk and delay-based decision-making, assessed with probabilistic and delay-discounting tasks. In well-trained rats, reversible inactivation of the medial OFC with baclofen/muscimol infusions increased risky choice on the probabilistic discounting task, irrespective of whether the odds of obtaining a larger/risky reward decreased (100–12.5%) or increased (12.5–100%) over the course of a session. This enhanced risky choice was associated with increased win–stay behavior, in which the rats exhibited an increased tendency to choose the risky option after being reinforced for the risky choice on the preceding trial. In contrast, acute medial OFC inactivation did not alter delay discounting. These findings suggest that the medial OFC plays a selective role in decisions involving reward uncertainty, possibly promoting the exploration of novel options when reward contingencies change. A comprehensive program of studies of the roles of other PFC and cingulate regions following their inactivation in probability discounting has highlighted the specific role of the medial OFC [79,80]. For example, inactivation of either the dorsal anterior cingulate cortex or the insula or the lateral OFC failed to affect probabilistic discounting (in the last case, unlike the results of Mobini et al. [63] following chronic lesions), although response latencies were slower following lateral OFC inactivation. By contrast, inactivation of the medial PFC (prelimbic) increased risky choice when reward probabilities were initially high, decreasing over the session, but had the opposite effect when the reward probabilities began low and increased subsequently [79]. This is perhaps consistent with a proposed role for adjusting decision biases in volatile situations. In their studies, St Onge et al. [80] showed that, whereas basolateral amygdala–accumbens circuits tended to drive choice toward the large, risky option, medial PFC–amygdala pathways promoted the opposite bias. Moreover, other structures, such as the lateral habenula, have been found to exert fundamental influences on probabilistic discounting, with inactivation essentially obliterating decisional factors influencing choice and leading to random responding [81].

A further complication applies when risky decision-making also involves possible punishment, eg, with electric shock, rather than reward omission as in the typical probability discounting paradigm. Setlow and colleagues have added punishing electric shock to the risk associated with high levels of reward. This paradigm appears more sensitive to manipulations of D2 receptors than probabilistic discounting, which simply depends on reward omission. Thus, Simon et al. [82] found that systemic D2 receptor agonists reduced risk-taking, whereas D1 agonists had no effect. Lower

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