1 An Introduction to Neural Systems

1.1 INTRODUCTION

The purpose of this book is to provide a comprehensive understanding of the neurobiology of social behavior in mammals, including humans. Social behavior, broadly defined, comprises those behaviors that are exhibited by conspecifics as they interact and includes both affiliative (prosocial) and antagonistic (antisocial) interactions. The social behaviors and processes that will be examined include aggression and competition, sexual behaviors, parental behaviors, the formation of social attachments, cooperation, and altruism. Each of these social behaviors will be analyzed across the different levels of investigation that have been used to study the behavior, from molecular neurobiology to neural circuits to functional magnetic resonance imaging (fMRI) data. The first two chapters of the book provide the necessary background in functional neuroanatomy (Chapter 1) and molecular biology and genetics (Chapter 2) that will serve as a foundation for a full appreciation of the neurobiology of social behavior that will be presented in the subsequent chapters.

One important aspect of this book is to uncover the neural mechanisms that determine whether social stimuli are assigned either a positive or a negative valence by the perceiver, with positive social stimuli activating neural pathways that cause contact seeking behaviors, acceptance, caregiving, and other prosocial behaviors, while negative social stimuli activate neural pathways that cause avoidance, rejection, competition, or even attack (antisocial behaviors). In other words, it may be valuable to view social behaviors as being influenced by two elementary neural networks: social stimuli can be processed by either an aversion/rejection network or an attraction/acceptance network, with such differential neural processing leading to different social outcomes [698]. Further, social stimuli may be automatically (innately) routed over either attraction or aversion networks, or such valence properties may be acquired through learning mechanisms. These core neural processes may then set the foundation for more complex social interactions. But what are the neural systems that regulate core approach and avoidance processes, processes that are embedded within and influence more complex social interactions? In what follows, an overview will be presented of functional neuroanatomy with an aim to explain such approach and avoidance systems in mammals. Animals approach or avoid a broad range of stimuli, not just social stimuli. Research findings will be presented from both social and nonsocial contexts with the understanding, which will be borne out in subsequent chapters, that there is overlap in the neural systems influencing social and nonsocial motivational processes (see [82]).
1.2 A SCHEMATIC OVERVIEW OF THE MAMMALIAN BRAIN

Based on the neuroanatomy in Swanson [951], Figure 1.1 depicts the general organization of the mammalian brain. Moving from rostral to caudal, the brain is broken down into two great divisions: the cerebral hemispheres (telencephalon) and the brainstem. Caudal to the brainstem lies the spinal cord. The cerebral hemispheres are divided into the cerebral cortex and the underlying, and therefore subcortical, cerebral nuclei. The cerebral cortex can be divided into isocortex (neocortex) and allocortex, with the former containing six well-defined cellular layers, while the latter contains less than six well-differentiated layers [951]. Isocortex makes up most of the occipital, parietal, temporal, and lateral prefrontal parts of the cortex. Examples of allocortex include the olfactory (piriform) cortex, parts of the amygdala, the hippocampal formation, and parts of the medial and orbital prefrontal cortex. Some important subcortical cerebral nuclei include the caudate nucleus (dorsal striatum), nucleus accumbens (ventral striatum), globus pallidus (dorsal pallidum), ventral pallidum, septal area, and some nuclei within the amygdala. The brainstem, upon which sits the cerebral hemispheres, is composed of the thalamus and hypothalamus (diencephalon), and the lower brainstem, which includes the midbrain, pons,
cerebellum, and medulla. Some of the lower brainstem nuclei that will be shown to play important roles in social behavior are the midbrain periaqueductal gray (PAG), dopamine neurons within the ventral tegmental area of the midbrain, and the serotonin neurons of the raphe nuclei located in the midbrain and pons. The term brainstem motor area (BSMA) will be used to refer to a group of nuclei in the lower brainstem with indirect and direct connections to cranial and spinal motor neurons. Most relevant with respect to the BSMA, the PAG and the midbrain locomotor region (located lateral to the PAG) both project to the medullary reticular formation, whose axons project to cranial and spinal motor neurons [361,420,1069]. As will become important, the descending projection of the midbrain PAG to the medullary reticular formation is an important route through which PAG output affects the display of reflex-like defensive and aggressive responses, such as behavioral immobility, escape responses, or biting, and reflexive responses related to sexual and parental behaviors.

1.3 FUNCTIONAL NEUROANATOMY

1.3.1 The Hypothalamus

1.3.1.1 Introduction

The three major functions of the hypothalamus are its regulatory influences over the autonomic nervous system and the pituitary gland, and its involvement in the control of a variety of motivated behaviors, including social behaviors [716,813,950]. Figure 1.2 shows a horizontal section through the hypothalamus, displaying its rostral-to-caudal and medial-to-lateral organization. With respect to its organization from medial to lateral, the hypothalamus contains a periventricular zone (which surrounds the third ventricle) and a medial and lateral zone. The periventricular zone contains those neurons primarily involved in neuroendocrine and autonomic regulation, while it is the nuclei of the medial and lateral zones that play dominant roles in the control of motivated behaviors, which involve influences over the somatic motor mechanisms that control both the reflexive and voluntary aspects of these behaviors.
The social behaviors influenced by the hypothalamus include reproductive behaviors (sexual and parental) and aggressive and defensive behaviors. As will be seen, it is likely that separate and distinct neuronal populations within the hypothalamus regulate different social behaviors.

Given the involvement of the hypothalamus in social and other motivated behaviors, one would expect that it would be a recipient of significant sensory inputs, and indeed this is the case [759,813]. The hypothalamus receives olfactory inputs from the amygdala and other olfactory areas. Afferents from the brainstem carry tactile and pain inputs, and the hypothalamus receives multimodal sensory inputs from the prefrontal cortex and from the hippocampus, the latter arriving either directly or indirectly via the septal area. Finally, an organism’s internal state importantly influences its social behavior, and primary among these internal factors are hormones. Neurons in the hypothalamus contain receptors for prolactin, estradiol, testosterone, progesterone, and adrenal corticosteroids [813,950]. A simple view is that hormones and other internal physiological stimuli bias how various sensory inputs are processed by the hypothalamus, which in turn affects the hypothalamic efferent pathways that are activated. With respect to social behavior, such effects would allow an organism to respond in one way or another to particular social stimuli, depending on the current hormonal milieu that is affecting the operation of specific neural circuits.

1.3.1.2 Motivation: Appetitive, Avoidance/Rejection, and Consummatory Behaviors

Several definitions of motivation exist [90,716,764,1021]. In its simplest definition, motivation is an internal process that modifies an organism’s responsiveness to a constant stimulus. That is, if an organism shows a change in the way it responds to a constant stimulus, some internal alteration must be mediating the behavioral change. As examples, food deprivation increases an organism’s responsiveness to food-related cues, the hormonal events associated with pregnancy termination increase a female’s responsiveness to infant stimuli, and gonadal steroids influence the occurrence of male and female sexual responses to sexual stimuli. Another definition of motivation refers to those internal processes that arouse and direct behavior toward a particular goal, giving rise to the term goal-directed behavior. Two major types of goal-directed responses are approach responses (also called appetitive or reward-seeking responses) toward a desired or pleasant stimulus, and avoidance or rejection responses toward aversive or noxious stimuli [868]. As will be described below, rejection responses can include approaching an aversive/unpleasant stimulus in order to attack it. The mechanisms underpinning such responses would define appetitive motivation and aversive motivation. Therefore, I am broadening the typical view of aversion to mean more than avoidance or withdrawal. An aversive stimulus is one that an organism does not like, and goal-directed responses can either avoid/escape from that stimulus or approach the stimulus to actively reject it.

In describing motivated behavior with respect to a desired or rewarding stimulus (one with a positive valence), such behavior can be separated into an appetitive goal-directed phase and a consummatory or terminal phase. During the appetitive or reward-seeking phase, the organism searches its environment to acquire the particular goal object. For example, a hungry animal will search for food, a sexually motivated organism will search for a mate, and a maternal female will seek out her infants or will search for displaced infants in order to transport them to a secure area. The consummatory phase is composed of those behaviors that occur once the desired goal is obtained, and the behaviors that occur during this phase are elicited by proximal cues from the goal object. Examples of consummatory responses toward a desired stimulus
are eating food, copulating with a mate, and nursing infants. Therefore, appetitive goal-directed behaviors reflect an underlying motivation, drive, or desire to engage in a behavioral interaction with a specific goal stimulus, while consummatory behaviors reflect the ability to perform specific behavioral responses once the goal object is attained.

Appetitive reward-seeking behaviors are variable, flexible, and can be influenced by learning and higher cognitive processes—the organism needs to search and possibly manipulate its environment in order to gain access to the desired goal. In contrast, consummatory responses are more reflexive in nature and are elicited by proximal stimuli from the goal object. A typical example is hunger and food intake. In response to the internal changes that result from food deprivation (lower energy supplies), food-seeking behaviors and food intake are activated. For the appetitive component, the organism will search its environment for food, relying on previous experience. The consummatory phase would be made up of the actual oral motor responses involved in ingestion.

In describing motivated behavior with respect to a noxious or aversive stimulus (one with a negative valence), it can similarly be separated into a goal-directed phase and a consummatory or terminal phase. In the case of defensive aggression, where an individual is threatened or attacked by another individual, the animal may attempt to use goal-directed responses to avoid or escape from the situation and to reach a safe location, but if cornered, she/he will engage in relatively stereotyped defensive/aggressive behaviors in response to the aggressive acts of the opponent. As will be elaborated upon in the chapter on aggression, male offensive aggression (for example, the aggression shown by a resident territory owner toward an intruder) can be similarly characterized as a response to an aversive (disliked) social stimulus that gives rise to both goal-directed and consummatory rejection responses. In this case, the territory owner approaches and chases the intruder (goal-directed rejection responses) and ultimately attacks the intruder (consummatory rejection responses) if proximal contact occurs.

Note that the definition of motivation as a change in responsiveness to a constant stimulus applies to both goal-directed and consummatory responses. A satiated animal will not search for food and will not eat food that is placed in its mouth. In contrast, the definition of motivation as a process that arouses and directs behavior toward a particular goal only applies to the proactive voluntary goal-directed phase of motivated behavior.

At this point, I would like to briefly indicate what I mean when I use the term *emotion*. On the one hand, this term will be used to refer to emotional behaviors, which are basically goal-directed and consummatory responses to aversive or noxious stimuli. However, for humans, this term will also be used to refer to those affective feeling states that occur throughout the pleasant-aversive continuum, with these experiential states being associated with goal-directed and consummatory responses to both pleasant and aversive stimuli. A discussion of feeling states will be reserved for humans, since we cannot measure such states in nonhuman animals.

In thinking about the neural underpinnings of the goal-directed and consummatory phases of motivated behaviors, because the goal-directed phase can be variable, flexible, and influenced by learning processes, it should involve telencephalic mechanisms. In contrast, the consummatory phase, which is stereotyped, reflexive in nature, and based on reactions to proximal stimuli, might be regulated primarily by lower brainstem mechanisms. Given the importance of the hypothalamus for motivated behaviors, to the degree that it is involved in both goal-directed and consummatory responses, one might predict that hypothalamic interactions with the telencephalon (i.e., cerebral hemispheres) regulate goal-directed responses, while hypothalamic interactions with the brainstem regulate
consummatory responses. A schematic diagram of these possibilities is shown in Figure 1.3. The involvement of telencephalic mechanisms would allow for more flexible, adaptive, voluntary responding through the use of higher integrative and cognitive processes. In conclusion, the hypothalamus may monitor and respond to an organism’s internal state and relay this information to the telencephalon, which then regulates strategic responses to the external environment based, in part, on this information.

Once a particular goal is achieved, proximal stimuli may activate hypothalamic neurons with descending projections to the brainstem that regulate specific consummatory responses.

1.3.1.3 The Hypothalamus and Neuroendocrine Regulation

Because of the important role of hormones in social behavior, a brief introduction to neuroendocrinology will be provided [677]. Figure 1.4 shows a schematic sagittal section through the basomedial hypothalamus and the attached pituitary gland. The periventricular zone of the hypothalamus contains most of the neurons that regulate the pituitary gland, which is divided into the anterior and posterior (neural) pituitary. When action potentials occur in those neurons that regulate the anterior pituitary, their neurochemicals (called neurohormones) are secreted into the primary capillary plexus located at the base of the hypothalamus. These neurochemicals then travel down the hypothalamic-pituitary portal veins to reach the secondary capillary plexus located in the anterior pituitary. From there, these neurohormones can reach cells in the anterior pituitary to affect the synthesis and release of additional hormones. Two examples of hypothalamic regulation of anterior pituitary function, which are relevant to the content of this book, will be presented. Gonadotropin-releasing hormone (GnRH; considered a hormone because even though it is released from axon terminals of a hypothalamic neuron in response to action potentials, such release occurs into the blood to affect nonproximal target cells in the anterior pituitary) affects the synthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from anterior pituitary cells. LH and FSH then circulate in the blood to reach the gonads where they regulate the synthesis and release of testosterone from the testes and estradiol and progesterone from the ovaries. The importance of the brain’s regulation of the pituitary is that it allows neural stimuli to affect the endocrine
FIGURE 1.4 The hypothalamus and neuroendocrine regulation. With respect to the posterior pituitary (neural lobe), oxytocin (OT) and vasopressin (AVP, arginine vasopressin) neurons in the paraventricular nucleus (PVN) of the hypothalamus send their axons directly to a capillary plexus (red overlapping circles) in the posterior pituitary. Since OT and AVP are released into the blood at this site, they act as neurohormones (NH). OT is shown as acting on the uterus, where it stimulates uterine contractions, and on the mammary glands, where it stimulates milk ejection. Other OT neurons, by synapsing on regular neurons (RN) within the brain, can release OT as a neurotransmitter (NT) or neuromodulator. Although not shown, AVP can also act as a neurotransmitter within the brain. With respect to hypothalamic control of the anterior pituitary, hypothalamic neurons secrete neurohormones into a primary capillary plexus located within the basomedial hypothalamus. These neurohormones then travel down the hypothalamic-pituitary portal veins to reach a secondary capillary plexus in the anterior pituitary gland, where they then influence the release of particular anterior pituitary hormones. In one of the examples of such neurohormone action, gonadotropin-releasing hormone (GnRH) stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. LH/FSH, in turn, stimulate estradiol and progesterone synthesis and release from the ovaries and testosterone synthesis and release from the testes. In the other example, CRH stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH, in turn, stimulates the synthesis and release of glucocorticoids from the adrenal cortex. Within the hypothalamus, neurons that release neurohormones are shown in red, while regular neurons that synapse on other neurons are shown in blue. The green- and red-filled circles in the anterior pituitary represent cells that secrete either ACTH or LH/FSH, respectively.
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A good example relates to breeding seasons. Some species are reproductively active only during certain times of the year. Very generally, changes in day length regulate the function of GnRH neurons. For species that breed in the spring and summer, increases in day length ultimately affect neural processes that activate GnRH neurons, which in turn stimulate LH and FSH release. Subsequent increases in testosterone and estradiol in the blood then enter the brain to activate the neural systems involved in sexual motivation and behavior. Another neurohormone that regulates the anterior pituitary is corticotropin-releasing hormone (CRH). CRH is produced by neurons in the paraventricular nucleus (PVN) of the hypothalamus (as well as by other neurons), and when it is released into the hypothalamic-pituitary portal veins, it affects the synthesis and release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH, in turn, acts on the adrenal cortex to stimulate the synthesis and release of glucocorticoids (corticosterone and cortisol). One function of glucocorticoids is their action on the liver to promote gluconeogenesis, which increases blood glucose levels. However, corticosterone and cortisol can also enter the brain to affect neural function and behavior. Stressful (aversive) stimuli (psychological stressors such as fear and anxiety-inducing stimuli and physical stressors such as noxious stimuli that cause pain) activate CRH neurons and the HPA axis (hypothalamo-pituitary-adrenal axis). The subsequent rise in blood glucose provides the organism with additional energy resources in such emergency situations. Not too surprisingly, glucocorticoid action in the brain also influences aggression-related neural systems.

The posterior or neural lobe of the pituitary is regulated differently from the anterior pituitary. Some neurons in the PVN and the supraoptic nucleus (SON) of the hypothalamus (SON is not shown in Figure 1.4), which manufacture oxytocin or vasopressin, send their axons directly to a capillary plexus located in the neural lobe. When PVN and SON neurons are activated, their action potentials release oxytocin and vasopressin directly into the blood. For the purpose of this brief introduction, the discussion will be limited to oxytocin. When oxytocin is released into the blood, it can act on peripheral targets such as uterine cells or myoepithelial cells in the mammary gland. Oxytocin is a hormone closely tied to the maternal condition. It acts on the uterus to cause uterine cells to contract and therefore aids the birth process. It is also crucial for the milk-ejection reflex—when a baby sucks on its mother’s nipple, neural pathways are activated that stimulate PVN and SON neurons to release oxytocin. The increases in blood levels of oxytocin reach the mammary gland, where they act on oxytocin receptors to cause the milk ducts to contract, which squirts milk into the baby’s mouth. The milk-ejection reflex is a perfect example of how neurohormones, in this case oxytocin, link the nervous system with the endocrine system.

In Figure 1.4, some neurons are labeled as regular neurons (RN). These are the typical neurons that we are most familiar with—they are activated by neurons and they release their neurotransmitter locally onto other neurons. The figure indicates that some PVN oxytocin neurons are regular neurons in that they synapse on other regular neurons instead of projecting to the capillary plexus in the posterior pituitary. That is, oxytocin can be released into the brain as a neurotransmitter or released into the neural lobe capillary plexus as a hormone. The same is true for vasopressin. Therefore, chemical structure does not define the difference between a hormone and a neurotransmitter, function does. If a neurochemical is released locally at a synapse, it is referred to as a neurotransmitter (or neuromodulator), but if the same chemical is released into the blood to act at a distant target, then it is called a hormone or neurohormone. As will be seen, oxytocin action in the brain plays a major role in regulating maternal behavior and other prosocial behaviors [703]. Oxytocin’s
action in parturition, milk ejection, and maternal behavior is a great example of an integrated neurochemical system—the peripheral effects of oxytocin as a hormone coincide with and support its role as a brain neurotransmitter that promotes maternal behavior.

1.3.2 Ernst and Fudge (2009): A Neural Model of Goal-Directed Motivational Processes

A review by Ernst and Fudge [272] will provide a starting point for a discussion of the role of the cerebral hemispheres in the regulation of goal-directed behaviors. In their Triadic Model, they propose that the ventral striatum (nucleus accumbens) plays a primary role in regulating goal-directed appetitive behaviors, while the amygdala regulates goal-directed avoidance responses. The prefrontal cortex is viewed as modulating or regulating the output from the amygdala and the ventral striatum so that an adaptive balance between the two systems is achieved. Starting with this simplified model, which proposes distinct functions for each of these areas, they acknowledge several qualifications, admitting that the amygdala and the striatum are heterogeneous structures and that each can regulate both appetitive approach and goal-directed avoidance responses. It is these qualifications that I want to emphasize in order to present a more complex view of the control of motivation. In what follows, a discussion of amygdala function will be presented, followed by a review of the ventral striatum and associated structures, and concluding with an analysis of the role of the prefrontal cortex in motivation.

1.3.3 The Amygdala

1.3.3.1 Basic Anatomy

The major components of the amygdala are similar in primates, cats, and rats. Figure 1.5 presents a cross-section through the rat amygdala showing some of its most important nuclei. With respect to the anatomy, a few points will be emphasized that are very relevant to social behavior [501,621,733,952]. First, the medial amygdala (MeA) receives strong olfactory inputs, and it, in turn, projects strongly to the hypothalamus via the stria terminalis. Different MeA neurons project to different parts of the hypothalamus, and these projection neurons have been found to either contain gamma-aminobutyric acid (GABA) or glutamate, as well as certain neuropeptides [95]. The central nucleus of the amygdala (CeA) receives a variety of sensory inputs, and it has important projections to the lateral hypothalamus (LH) and to the periaqueductal gray (PAG) in the midbrain. CeA is divided into a lateral and medial nucleus (CeAl and CeAm), and its neurons use GABA as a neurotransmitter. CeAm is the major projection nucleus of CeA, with efferents to LH and PAG. The lateral, basolateral, and basomedial nuclei (LA, BLA, BMA) of the amygdala receive olfactory, gustatory, auditory, visual, and somatic sensory inputs from isocortex and allocortex, although simple visual and auditory stimuli may reach the amygdala directly from the dorsal thalamic sensory relay nuclei. The major projection neurons of the lateral and basal amygdala nuclei use glutamate as their neurotransmitter. One projection of BLA is to the CeAm, allowing for a BLA-CeAm-LH or BLA-CeAm-PAG circuit. However, the BLA and BMA also have strong projections to the ventral striatum (VS) and associated areas. To the extent that BLA/BMA neurons influence motivation, one might predict that BLA-CeAm-PAG projections mediate consummatory type responses, while BLA/BMA-VS projections mediate goal-directed responses. That is, projections from the amygdala that go directly to the brainstem may regulate simple, reflex-like responses, while projections to other nuclei within the cerebral hemispheres, such as VS, may regulate more strategic and voluntary goal-directed responses. Finally, the amygdala has significant reciprocal connections with the...
FIGURE 1.5 The major nuclei of the amygdala. The upper diagram shows a frontal section through the rat brain, with the amygdala and nearby regions outlined by a dashed box. An expanded view of the amygdala is shown in the lower diagram. Abbreviations: BLA = basolateral amygdala; BMA = basomedial amygdala; CeAm = medial part of the central nucleus of the amygdala; CeAl = lateral part of the central nucleus of the amygdala; CoA = cortical nucleus of the amygdala; CP = caudate/putamen; IC = internal capsule; ITC = intercalated nuclei of the amygdala; LA = lateral nucleus of the amygdala; MeA = medial nucleus of the amygdala; OT = optic tract. The upper frontal section is modified from Swanson LW. Brain maps: Structure of the rat brain, 2nd ed. Amsterdam: Elsevier, 1998/1999.
prefrontal cortex (PFC), and the nature and importance of these connections will be a major focus of this chapter and other parts of this book.

In addition to these major connections, there are also groups of local inhibitory GABAergic neurons within the amygdala, which when activated, can restrain the efferent outputs just described. The axons of these local inhibitory neurons do not leave the amygdala, and their cell bodies are contained within LA, BLA, BMA, CeAl, and in the intercalated nuclei (ITC) of the amygdala [918].

Note the apparent difficulty that this anatomy presents for the Triadic Model of Ernst and Fudge [272]. If BLA/BMA neurons are involved in avoidance and the VS is involved in appetitive approach, what might be the function of BLA/BMA glutamatergic projections to VS?

### 1.3.3.2 Functional Anatomy of the Amygdala: Reflexive Fear Responses

The work of LeDoux [530] has emphasized the role of the amygdala in fear-related processes. The primary focus of LeDoux’s research has been on consummatory (reflexive) defensive responses rather than goal-directed avoidance responses, and this research has examined the neural circuitry underlying the conditioned fear response (CFR). The CFR involves a Pavlovian learning procedure—a conditioned stimulus (CS), such as a neutral tone, is paired with an aversive or noxious unconditioned stimulus (US), such as foot shock. After several pairings of the CS with the US, the CS acquires the ability to elicit a CFR. The particular CFR that has been the object of many studies in rodents is the freezing response—initially the tone does not cause inhibition of movement, but after several CS–US pairings, the CS begins to elicit the freezing response, where the animal becomes immobile. There is a tremendous amount of recent research of the neurobiology of the CFR, but only certain aspects will be highlighted here [20,190,267,407,545,1076]. It has been shown that plasticity within an LA-BLA-CeA-PAG circuit is necessary for the ability of a tone that has been paired with shock to inhibit motor activity in an experimental animal. The classic research on fear conditioning indicated that LA was the primary site where associations between the CS and the US are formed, while CeAm output projections to PAG were necessary for the behavioral expression of CFRs. Although LA does not project directly to CeAm, it influences CeAm indirectly through projections to BLA. Figure 1.6(A) shows a simplified neural circuit for the formation of the CFR of freezing. As a result of CS–US pairings, synaptic plasticity mechanisms strengthen the synapse from the CS sensory input arriving from either the cortex or the thalamus, onto LA neurons, which then results in the CS activating an LA-BLA-CeAm-PAG circuit that results in somatomotor inhibition (the PAG has descending projections to the medullary reticular formation; [420]). Figure 1.6(A) also indicates the neural circuits that, if active, could restrain the output of CeAm and therefore suppress the CFR [20,190]. Certain BLA glutamatergic neurons project to either CeAl or ITC, and these neurons then send GABAergic projections to CeAm that inhibit its output. Three points are worth noting. First, different populations of BLA neurons can either promote or depress reflexive fear responses mediated by CeAm output. Second, any stimulus that activates those ITC and/or CeAl neurons that synapse on CeAm projection neurons is in position to depress fear responses. Third, uncovering the microcircuitry within a neural region is essential for an understanding of the ways in which its projection neurons, which connect to other brain regions (such as PAG), are regulated.

When the role of oxytocin in social behavior is examined in several future chapters, it will show that one of the effects of oxytocin when it is released into the brain as a neurotransmitter is that it has anxiolytic effects—it can decrease fearfulness. In this context, the impressive work
of Stoop and colleagues [431,932,999] is relevant to the current discussion of amygdala microcircuitry. Oxytocin receptors are located in CeAl, and oxytocin activates CeAl neurons that, in turn, inhibit CeAm neurons that project to PAG. In behavioral studies, they found that oxytocin microinjection into the CeA suppresses the CFR in rats.

The studies reviewed above have analyzed the amygdala’s involvement in CFRs. A recent study has explored the amygdala microcircuitry underlying an unconditioned or innate anxiety response in mice that were tested on the elevated plus maze [982]. The elevated plus maze consists of a central start box that connects to either closed arms or alleys (the alleyway has walls) or to open arms without walls. Rodents display anxiety-like responses in open spaces; if a mouse spends a lot of time in the open arms of the maze, this is usually interpreted as indicating a low level of anxiety or fear of open novel spaces, while a decreased amount of open arm exploration time would be interpreted as an enhancement of fearfulness. Tye et al. [982], using optogenetic techniques (see Box 1.1), found that when mice received photostimulation of the BLA, they showed decreased open arm exploration, suggesting an increase in fearfulness. In contrast, selective photostimulation of BLA axon terminals in CeAl resulted in an anxiolytic effect, with such mice spending more time in the open arms compared to control mice. Subsequent in vitro brain slice optical stimulation coupled with electrophysiological recordings indicated that two separate populations of neurons in BLA project to CeA—one to CeAl and one to CeAm. Direct photostimulation of the entire BLA had a net excitatory effect on CeAm, which would presumably activate CeAm projections to PAG, leading to movement suppression. In contrast, photostimulation of BLA axon terminals in CeAl would activate GABAergic inhibitory projections from CeAl to CeAm, in this way depressing the unconditioned fear response to the open arms. The authors conclude that the

**FIGURE 1.6** (A) The classic neural model of the conditioned fear response (CFR). Initially, a neutral tone does not cause an animal to become immobile (freezing response). However, after a tone conditioned stimulus (CS) is paired with shock (the unconditioned stimulus; US) over several trials (a time line depicting CS–US presentations is shown on the left under the lateral nucleus of the amygdala = LA), the CS acquires the ability to elicit freezing. Neural activity derived from the CS and US converge on LA, with the result that the synapse that relays sensory input from the CS to LA is strengthened (surrounded by a dashed line). LA neurons then excite neurons in the basolateral amygdala (BLA), which in turn excite neurons in the medial part of the central nucleus of the amygdala (CeAm). CeAm activates the periaqueductal gray (PAG), which, through its descending projections, causes the freezing response. Since CeAm neurons are GABAergic (inhibitory), CeAm is shown as activating the output of PAG to the lower brainstem by inhibiting local inhibitory neurons within PAG. The neural pathways shown in dashed lines are NOT active during the CFR. However, if they were active, they would inhibit the CFR; additional neurons in BLA project to intercalated nuclei (ITC) and to the lateral part of CeA (CeAl), and these latter nuclei (shown in red), when active, inhibit CeAm output, with the result that the CFR would be depressed. Axons ending in a bar
balance between the direct and indirect inputs of BLA to CeAm regulate the final output of CeAm and the level of fearfulness that is exhibited.

Most of the research on these reflexive-type fear responses has been performed in rodents. However, the CeA also appears to be an important output region regulating simple fear responses in rhesus monkeys. For example, monkeys with bilateral excitotoxic amino acid lesions of CeA reach for a preferred food item in the presence of a snake with a much shorter latency than do intact control monkeys [470]. An important human example is the case of SM, a 44-year-old woman (in 2010) with extensive bilateral amygdala damage resulting from Urbach–Wiethe disease, which is a genetic disorder that causes abnormal calcification of the amygdala, resulting in lesions [287]. The exact age of onset of her amygdala damage is not known with certainty, although it is likely to have been a long-term lesion. SM was examined under a variety of naturalistic test conditions that were expected to arouse fearfulness, such as visits to an exotic pet store that had snakes and spiders, and to a commercial “haunted” house. Compared to controls, SM showed a relative absence of fear responses (she approached and handled snakes and she did not scream when surprised by “monsters” in the haunted house). Importantly, she also reported that she did not experience fear in these situations. When neuroscientists study nonhuman animals, we can only

represent inhibitory connections, and those ending in an arrow are excitatory. (B) The potential neural circuitry underlying goal-directed active avoidance or escape responses. The CFR is a reflexive consummatory response, and the elicited freezing response does not avoid or escape shock. To avoid or escape from shock, neural pathways would have to inhibit freezing while also promoting goal-directed active responses. This could occur if an aversive or noxious stimulus activated BLA neurons with excitatory projections to CeAl, which would then inhibit CeAm. Further, aversive stimuli could also activate BLA neurons that project to the ventral striatum (VS = nucleus accumbens), which would lead to goal-directed avoidance or escape responses. Axons ending in a bar represent inhibitory connections, and those ending in an arrow are excitatory.

examine and measure their behavior, and we have no access to what they may be experiencing. In contrast, with people, we can interview them and ask them about their affective states. I will have more to say about SM later, and I will also discuss the putative neural underpinnings of emotional experience.

1.3.3.3 Functional Anatomy of the Amygdala: Goal-Directed Avoidance Responses

Up to this point, I have been primarily examining the role of the amygdala in simple reflexive-like conditioned and unconditioned fear responses, and I have emphasized the importance of amygdala output projections to the brainstem in mediating such responses (i.e., CeAm to PAG). What about goal-directed avoidance or escape responses? The amygdala, not surprisingly, is involved in these as well, and the important projections appear to connect the amygdala with other parts of the cerebral hemispheres. BLA projections to the cerebral hemispheres include projections to ventral striatum and prefrontal cortex; perhaps these projections are important for goal-directed avoidance and escape responses. In this context, consider the following scenario. You are in a dark alley, and in the distance you see a suspicious individual carrying a knife. Initially, you might attempt to avoid this person and escape from the situation. However, if the person chases and catches you, you might engage in reflexive defensive behaviors. In this scenario, perhaps the dominant neural activity would switch from BLA projections to VS or PFC to CeAm projections to PAG as the behavior changed from goal-directed avoidance to defensive responses. In an interesting human study, there is evidence that this switch in neural activity does indeed occur under such a situation [654]. With respect to the role of the amygdala in fearfulness, while BLA projections to CeAm may regulate consummatory or simple fear and defensive responses, BLA projections to CeAl may inhibit consummatory defensiveness.
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BOX 1.1

OPTOGENETIC METHODS AND NEURAL CIRCUITRY ANALYSIS

The development and use of optogenetic methods over the past decade have greatly increased our understanding of how specific phenotypically defined neural circuits regulate behavior. Excellent overviews of this method have been written [981,1056,1057], and only a brief introduction will be provided here. (Aspects of this presentation will be more fully appreciated after reading the sections on the amygdala and basal ganglia in this chapter and Chapter 2 on genetics.)

This method combines the use of optical and genetic techniques so that specific neural circuits can either be stimulated or inhibited by light. In a typical experiment, a genetically modified virus carrying a microbial opsin gene is stereotaxically injected through an implanted guide cannula into a specific neural region. The virus is then incorporated into the genome of the neurons within the injection site. Where possible, the promoter region of the opsin gene is constructed so that the opsin is only expressed within certain types of neurons. However, some promoter sequences that would be needed to limit opsin expression are too large to be packaged in viral vectors. In such cases, more advanced strategies, which involve the use of transgenic mice, are needed to restrict expression to specific neurons.

The two most commonly used opsin genes that have been injected into the brain are channelrhodopsin 2 and halorhodopsin. When channelrhodopsin 2 is expressed within a neuron, it produces a cation ion channel that is sensitive to blue light; when activated by blue light, the ion channel opens, allowing Na⁺ ions to enter the neuron to cause an excitatory depolarization. In contrast, halorhodopsin produces a Cl⁻ ion pump protein that is incorporated in the cell membrane of neurons and is activated by yellow light. When activated, the pump moves Cl⁻ ions into the neuron, hyperpolarizing and therefore inhibiting neural activity. Importantly, when these opsins are expressed, they are incorporated into the cell membrane throughout a neuron and, therefore, they are not only present in cell bodies and dendrites but are also expressed within axons and axon terminals. Since any one neuron may synapse in several brain regions, optogenetic techniques allow one to selectively excite or inhibit specific axon terminals by directing a light stimulus at the terminal rather than the cell body. A light stimulus is usually introduced into the brain by lowering a thin fiber-optic wire that is coupled to a light source, such as a laser, into the selected brain region through a previously implanted guide cannula.

Three studies will be described that have employed optogenetics to understand the neural circuits that underlie behavior. These studies relate to the content of this chapter, and relevant figures in this chapter will be utilized to explain the rationale and method of each study. In reference to Figure 1.6, research on the CFR proposes that the site of neural plasticity is within LA. That is, when a tone is paired with a shock, the ability of tone synaptic inputs to activate LA projection neurons (pyramidal neurons) is strengthened. Using optogenetic techniques, Johansen et al. [458] (also see [459]) set out to test this hypothesis. A modified viral vector was stereotaxically injected into LA of rats. The virus contained the channelrhodopsin 2 gene with a CaMKII (calcium modulated kinase II) promoter sequence, which was meant to restrict expression of the gene to pyramidal cells and avoid expression within inhibitory GABA interneurons. Subsequently, the attempt was made to condition the rats using blue light stimulation of LA as the US. A tone was paired with light stimulation of the LA
over several trials, and it was determined whether a CFR (behavioral immobility) occurred to the tone stimulus alone. The results indicated that this paradigm did lead to the development of a CFR but that the strength of the conditioning (amount of time spent freezing) was weak in comparison to the normal conditioning paradigm where the tone would be paired with shock. The weakness of the conditioning might be explained as follows. Although channelrhodopsin 2 expression may have been restricted to the LA pyramidal cells, it would be expressed in all such cells, and therefore would have included both positively and negatively valent neurons and LA neurons that were part of more than one circuit. Therefore, the stimulated LA neurons may not only have been part of an aversive LA-to-BLA-to-CeAm-to-PAG circuit, but could also have been part of aversive or appetitive circuits that ultimately projected to the NA-VP circuit. This lack of specificity probably diluted the observed effects.

In an outstanding study, Knobloch et al. [502] explored the anxiolytic effects of oxytocin within CeAl of the amygdala by using optical stimulation of OT axon terminals in this region. A viral vector that contained the channelrhodopsin 2 gene coupled to the OT gene promoter sequence was injected into the PVN of the hypothalamus. This promoter sequence restricted the expression of the opsin to oxytocin neurons. These opsin-containing OT neurons were shown to project to a variety of brain regions, including the amygdala. In vitro studies showed that blue light stimulation of axons in the CeAl region was associated with OT release and with increased neural excitation in CeAl neurons. This activation subsequently inhibited CeAm neurons (see Figure 1.6). Recall that the output of CeAm to PAG mediates the CFR. In vivo studies, in rats that had previously been conditioned, showed that blue light stimulation of CeAl inhibited the CFR. The above studies used rats and the injection of a modified viral vector into a specific brain region. More complex studies have combined microinjections of modified viral vectors into the brains of transgenic mice (see Chapter 2). Such approaches are used when viral vector modification alone cannot fully limit the expression of an opsin to a specific neuron type. In reference to Figure 1.8, which describes the operation of the dorsal basal ganglia, research has suggested that activation of the direct pathway stimulates, while activation of the indirect pathway inhibits, movement. Kravitz et al. [509] used optogenetic techniques with transgenic mice to prove this mechanism of operation. This study utilized Cre recombinase transgenic mouse lines. The D1-Cre strain expressed the Cre recombinase protein under the control of the D1 dopamine receptor gene promoter, and therefore would only be produced in neurons that contained the D1 receptor. The D2-Cre transgenic mouse line only expressed the Cre recombinase protein in neurons that contained the D2 dopamine receptor. For each strain, a modified viral vector containing the channelrhodopsin 2 gene was injected into the dorsal striatum (caudate-putamen). The opsin gene was flanked by a pair of DNA sequences referred to as lox sites. The Cre/lox recombination mechanism works as follows: in those neurons that express Cre recombinase, the recombinase protein recognizes the lox sites and operates to splice the lox-flanked gene into the genome of the Cre recombinase-expressing neuron. Therefore, in the D1-Cre strain and the D2-Cre strain, channelrhodopsin 2 was expressed in either the direct pathway D1-containing neurons or the indirect pathway D2-containing neurons, respectively. As predicted, blue light stimulation of the dorsal striatum of the D1-Cre strain stimulated movement, while blue light stimulation of the dorsal striatum inhibited motor activity in the D2-Cre transgenic mice.
via a depression of CeAm output to PAG, which would then allow BLA projections to either VS or PFC to regulate goal-directed and complex avoidance and escape strategies [352,654]. See Figure 1.6(B).

In support of the above neural model, several studies in rodents that have employed neuron-specific excitotoxic amino acid lesions of different amygdala nuclei have shown that lesions of BLA disrupt a previously learned instrumental avoidance response, while lesions of CeA are without effect [183,482]. In the Choi et al. [183] study, rats were trained in a two-way active avoidance paradigm where they learned to shuttle back and forth in an alleyway in order to avoid a shock that was predicted by a tone. Most rats acquired this response, although about 20% showed poor learning because they tended to freeze when the tone came on and therefore did not run down the alley to avoid the shock. These latter rats appeared to only show the CFR (Pavlovian learning), which interfered with the learning of the instrumental goal-directed active avoidance response. For the 80% of rats that learned well, post-learning lesions of BLA, but not CeA, disrupted the avoidance response to the tone. Importantly, for the 20% of rats that were poor learners of the active avoidance response, subsequent lesions of CeA allowed the instrumental response to be learned. Killcross et al. [482] suggest that the processing of aversive stimuli through a BLA-to-VS circuit may allow for goal-directed instrumental avoidance responses. Figure 1.6(B) summarizes the potential neural circuitry through which threatening or aversive stimuli might lead to goal-directed avoidance and escape responses.

1.3.3.4 Functional Anatomy of the Amygdala: Goal-Directed Appetitive Responses

The involvement of the amygdala in goal-directed avoidance behavior fits with the model presented by Ernst and Fudge [272]. But there is also evidence that the amygdala is involved in goal-directed appetitive responses [501]. Research shows that BLA damage produces deficiencies in the ability of stimuli that have been paired with a primary reward to maintain instrumental or operant responding when the primary reward is remote in time. This, to me, is a good definition of goal-directed appetitive behavior, where an organism responds to stimuli that predict rewards in order to ultimately obtain the reward, which then leads to consummatory responses. Everitt, Cador, and Robbins [276] showed that excitotoxic amino acid lesions of BLA disrupted a male rat’s instrumental responding (an operant bar press response) to gain access to a sexually receptive female. In a study by Simmons and Neill [904], male rats were trained to obtain a food reward on an FR (fixed ratio) 16 operant conditioning schedule of reinforcement. Once a stable baseline rate was established (learning had occurred), bilateral injections of muscimol were administered into the BLA. Muscimol is a GABA-A receptor agonist that temporarily inactivates neurons by mimicking the inhibitory neural effects of GABA. The animals were then placed in the operant chamber and their responses were measured over 20 min. Muscimol produced a dose-related decrease in lever presses. In contrast, muscimol injections into the BLA did not affect the amount of food ingested during a 30-min free feeding session. These findings conform to the idea that muscimol in BLA depressed appetitive goal-directed reward seeking behavior but did not affect the consummatory response that is regulated by direct contact with proximal food cues. Therefore, the BLA appears to be part of a neural network that controls whether an organism will work, and how much energy will be devoted, to achieve a desired goal: appetitive or reward-seeking behavior (also see [24]). As will be shown shortly, such appetitive amygdala circuits connect the amygdala to other...
regions in the telencephalon, such as the ventral striatum and related structures.

1.3.3.5 **Functional Anatomy of the Amygdala: Distinct Neural Circuits That Respond to Either Positively or Negatively Valent Stimuli**

Because of the involvement of the amygdala in both goal-directed avoidance and appetitive behaviors, I take a labeled line view of the amygdala, which proposes that distinct neural circuits within the amygdala carry specific types of information. A variety of sensory stimuli reach the amygdala from the cerebral cortex. Some stimuli are innately noxious or threatening, and others are innately attractive and appealing. Still other stimuli gain aversive or appetitive characteristics as a result of being paired with innate positive or negative stimuli. Aversive, noxious, or unpleasant stimuli are proposed to activate one population of amygdala neurons, the efferent projections of which can give rise to goal-directed avoidance, escape, or rejection responses. I will refer to these amygdala neurons as those with a negative valence, since they code for unpleasant stimuli. In contrast, reward-related or appetitive stimuli activate positively valent amygdala neurons whose efferents can give rise to goal-directed appetitive responses. In this view, the amygdala regulates both goal-directed appetitive and avoidance responses, based on the circuits activated by particular stimuli. Some interesting neurophysiological data support these views.

Belova, Paton, and Salzman [84] recorded the neural activity of single neurons within the amygdala from rhesus monkeys as they were exposed to different visual stimuli that were paired with either liquid rewards or aversive air puffs into the eye. Monkeys were trained to focus on the center of a screen for 1 s, and then a neutral visual image was presented for 300 ms. Then 1.5 s later, a liquid reward for some stimuli or an aversive air puff for other stimuli was presented. After the monkeys learned the initial value or valence (+ or −) of each visual image (when the monkeys expected the liquid reward they engaged in anticipatory licking behavior; when they expected the air puff, they blinked), the researchers reversed the image value assignments. During reversal, the initial positive image was followed by an air puff, and the initially negative image was followed by a reward. The basic findings can be outlined as follows:

1. With respect to the US, liquid reward activated one population of neurons in the amygdala, while air puffs activated a separate population of amygdala neurons. One might call these innate + and − stimuli that activate positively or negatively valent amygdala neurons, respectively.

2. Once the monkey learned the relation between a visual stimulus and a reward, that visual stimulus activated the positively valent neurons. When conditions reversed, so that the previously rewarded visual stimulus was followed by an aversive air puff, the response of the positively valent neuron to that visual stimulus declined. In contrast, a separate population of amygdala neurons responded to visual stimuli paired with air puffs, but the response of these negatively valent amygdala neurons to that visual stimulus declined once reversal training occurred so that the visual image was followed by a reward rather than an air puff. These results indicate that neurons in the amygdala encode stimulus value or valence, and neurons that respond to positive or pleasant stimuli are separate from those that respond to negative or aversive stimuli.

3. Reconstruction of electrode location via magnetic resonance imaging (MRI) analysis indicated that neurons that responded to either positive or negative stimuli were located in BLA as well as other amygdala regions.
Schoenbaum, Chiba, and Gallagher [869] performed a similar single neuron recording study on rats. Water-deprived rats had to sample an odor presented in a port on each trial (odor sampling) in order to decide whether to respond (go response) at a nearby fluid well. A go response resulted in delivery of a rewarding sucrose solution after the presentation of a “positive” odor, or an aversive quinine solution after the presentation of a “negative” odor. Rats would begin each session by responding on every trial, irrespective of whether a positive or negative odor was presented. Learning was evident when a rat began to withhold responses (no-go) after sampling the negative odor in order to avoid quinine delivery. Neural activity was recorded during odor evaluation trials after the rat had learned the associations (responding to the + odor and not to the − odor). Within the BLA, some neurons had higher rates of firing during evaluation of odors that predicted sucrose delivery when compared to their rates when “negative” odors were sampled, whereas other neurons responded more strongly during evaluation of cues that signaled quinine delivery. Importantly, during reversal learning, if a neuron responded to a “positive” odor that was reversed to a “negative” odor, over a series of trials that neuron ceased to respond strongly to the now negative odor. Therefore, a neuron’s selectivity was not tied to the sensory features of a particular odor but rather depended on the associated outcome. Importantly, when BLA neurons developed selective responding during odor sampling, this selectivity (difference between rate of firing to positive versus negative odor) was not present during early training trials but developed rapidly, well before accurate choice performance was achieved, which suggests that neural activity was a measure of stimulus valence rather than a measure of a particular motor response (go versus no-go).

In a related study, Shabel and Janak [883] recorded from single neurons in the rat amygdala and found three classes of neuronal responses. As in the above studies, some neurons responded selectively to appetitive stimuli, while others responded selectively to aversive stimuli. A third class of neurons responded to both appetitive and aversive stimuli. This latter class might be considered arousal neurons that signal motivational and emotional salience independent of valence.

Most of the discussion so far has concentrated on the BLA and CeA. However, MeA also contains separate populations of neurons that respond to stimuli with either a positive or negative valence. MeA receives strong olfactory input, and research on rodents shows that predator odors activate one group of MeA neurons that project to hypothalamic regions that regulate defensive and escape responses, while sexual pheromones activate another group of MeA neurons that project to different hypothalamic regions that regulate reproductive behaviors [184]. When I argue for a labeled line point of view, it is basically a localization of function point of view. Within the brain regions that influence motivation and emotion, different circuits have different functions, in a manner similar to the sensory systems, where, for example, the function of lateral geniculate nucleus projections to visual cortex is distinct from medial geniculate nucleus projections to the auditory cortex.

The results of these amygdala studies are important for several reasons. Not only do they indicate that the amygdala contains separate neurons that respond to aversive or appetitive cues, but they also show that experience with an initially neutral stimulus, due to learning processes, can result in that stimulus acquiring either a positive or a negative valence. Let’s put this in the framework of understanding social behavior. When you first meet someone, your emotional/motivational response may be neutral. However, after some social interactions, that person’s stimuli may gain the ability to activate either positive or negative amygdala neurons, depending on the outcomes of your interactions with that person.
Although I have mainly discussed the role of the amygdala in motivational and emotional contexts that did not involve social behavior, these studies are clearly related to the role the amygdala might play in social behaviors, and in subsequent chapters this view will be strongly affirmed. At this point, I will note that fMRI studies (Box 1.2) in humans show that the amygdala can be activated by both positive and negative social stimuli, such as angry or happy faces [251]. Further, the human patient SM, who has bilateral amygdala damage, shows deficits in social behaviors, although these deficits are not extreme [6,398,771]. SM has a long-standing amygdala lesion, and Phelps and LeDoux [771] point out that she may not show pervasive and severe social deficits because of compensatory mechanisms resulting from a lifetime of social interactions, which may have allowed other parts of the brain to regulate a certain level of social responsiveness. Further, social knowledge obtained through social interactions that occurred prior to the formation of the calcified amygdala lesion may have allowed for certain aspects of appropriate social behavior, particularly if such social information was stored in brain regions outside the amygdala. Interestingly, however, in a study by Heberlein and Adolphs [398], when SM and normal control subjects were shown films of inanimate objects (triangles and squares) interacting, normal subjects spontaneously created social narratives of these interactions (anthropomorphizing), while SM did not. One interpretation is that SM has permanent deficits in automatic or immediate social processing. Finally, the social behavior of individuals with Williams syndrome (WS) is relevant. WS is a human genetic disorder caused by the hemizygous deletion of about 25 genes from chromosome 7 [447]. In comparison to normal controls, WS individuals are characterized by hypersociality—they are gregarious and empathic and show no fear of strangers [461]. Haas, Mills, Yam, Hoeft, Bellugi, and Reiss [372], in an fMRI study, found that WS subjects, in comparison to controls, showed increased amygdala activation to happy faces and decreased amygdala activation to fearful or angry faces (also see [638]). Since amygdala activation to threatening nonsocial stimuli was not altered, these findings appear specific to social stimuli. The genetic deletion appears to have affected the functional activity of positively and negatively valent amygdala neuron connectivity with other parts of the brain [372,447], resulting in a facilitation of amygdala prosocial circuits and a depression of amygdala circuitry related to social aversion, withdrawal, and rejection.

1.3.4 The Dorsal and Ventral Basal Ganglia and the Influence of the Nigrostriatal and Mesolimbic Dopamine Systems

1.3.4.1 Introduction

In the Ernst and Fudge model [272], the ventral striatum (nucleus accumbens) was given a special role in the regulation of goal-directed appetitive responses. However, just as the amygdala was shown to be involved in both appetitive and aversive motivation, the same appears to be true for the ventral striatum. In order to critically evaluate this proposal, an overview of two important neural systems within the subcortical cerebral hemispheres is needed: the dorsal basal ganglia and the ventral basal ganglia, each of which receives significant dopaminergic input from the brainstem [434].

The midbrain gives rise to several major ascending DA systems that terminate in the cerebral hemispheres, and two of these are the nigrostriatal and the mesolimbic DA systems. Although there is some overlap in the organization and function of these systems, the nigrostriatal DA system primarily modulates functional activity within the dorsal basal ganglia, while the mesolimbic DA system primarily modulates activity within the ventral basal ganglia.
1. AN INTRODUCTION TO NEURAL SYSTEMS

BOX 1.2

UNDERSTANDING THE FMRI BOLD SIGNAL

Much research dealing with human social, cognitive, and emotional neuroscience utilizes the indirect measurement of neural activity in the brain under specified conditions through functional magnetic resonance imaging (fMRI; [734]). In a typical cognitive or affective neuroscience fMRI scanning procedure, a subject is placed in a scanner and a magnetic field is passed through the head region and brain while the subject performs a specified task, such as observing visual scenes (for example, angry, happy, or neutral faces). The scanner measures a hemodynamic response in the brain referred to as the blood-oxygen-level dependent (BOLD) signal. The BOLD signal is based on the differential magnetic properties of oxygenated and deoxygenated hemoglobin. The following sequence of events is usually considered to result in an increased BOLD signal [42,43]: as neural activity increases in a particular brain region, increases in local cerebral blood flow occur in that region. This increased blood flow results in an increase in the oxygenated-to-deoxygenated hemoglobin ratio, which results in an increase in the measured BOLD response.

Given that the BOLD signal is an indirect measure of neural activity within a brain region, an important question is the nature of the neural activity that is correlated with the BOLD signal. Research on primates and rodents, which has combined optogenetics, electrical recording, and fMRI procedures, has provided some answers [32,536,798]. The BOLD signal is positively correlated with the amount of synaptic input to a neural region, the degree of neural processing within both excitatory and inhibitory local circuit neurons within the region, and the amount of neural activity in the output or projection neurons through which the region of interest connects to other neural regions. Importantly, it has been clearly shown that an increased BOLD signal can occur in a brain region even though there is no increase in the activity of the projection neurons [32,798]. The following figure shows two cases where an increased BOLD signal (above a baseline control value) would be detected in two different brain regions, but in one case (Area 1) the output of a region would be increased and in the other (Area 2) the output would be decreased. In this figure, axons with a solid line are highly active (HI), while those with a dashed line are exhibiting low activity. Therefore, an increased BOLD signal in each of the boxed areas does not necessarily mean that the output of each brain region has increased. Indeed, its output to other brain regions may have actually decreased.

In the context of this understanding, note that statistical procedures have been applied to fMRI data in order to get a measure of the
As shown in Figure 1.7, the nigrostriatal DA system originates in the substantia nigra pars compacta (SNc) and terminates in the caudate nucleus and putamen, which are collectively referred to as the dorsal striatum. Nigrostriatal DA input to the dorsal striatum facilitates an organism’s behavioral reactivity to sensory stimuli that are primarily of isocortical origin. In contrast, the mesolimbic DA system originates from neurons in the ventral tegmental area (VTA) of the midbrain, and one of its major sites of termination is the nucleus accumbens (NA) or ventral striatum. One of the functions of the mesolimbic system is to facilitate an organism’s behavioral reactivity to sensory stimuli that are primarily being relayed to the NA from neural regions that have been referred to as components of the limbic system: amygdala, hippocampus, and allocortical parts of the prefrontal cortex [91]. Mogenson [655] referred to this system as the limbic motor system, and DA input to NA was viewed as increasing an organism’s responsiveness to stimuli that have motivational and emotional significance. For example, since the BLA projects to NA [1044], one might conclude that DA input to NA facilitates responding to stimuli that NA receives from BLA, and that such behavioral reactivity might include either goal-directed appetitive responses or goal-directed avoidance responses, depending on whether BLA is relaying stimuli with a positive or negative valence.

1.3.4.2 Detailed Analysis of the Operation of the Nigrostriatal DA System and the Dorsal Basal Ganglia

Although my focus will be on the ventral basal ganglia, which includes the ventral striatum, because much more research has been done on the organization and function of the dorsal basal ganglia, an overview of its operation will be presented first and then compared to the ventral basal ganglia. Figure 1.8 shows a schematic of dorsal basal ganglia neural circuits...
The nigrostriatal DA system

Sensory input → Isocortex (neocortex) → Caudate → Putamen → Behavioral response

Dorsal striatum

SNc DA Behavioral response

The mesolimbic DA system

Sensory input → Amyg Hipp PFC → NA → Behavioral response

Ventral striatum

VTA DA Behavioral response

FIGURE 1.7 A simplified differentiation between the functional neuroanatomy of the nigrostriatal dopamine (DA) system and the mesolimbic DA system. For the nigrostriatal system, DA input to the caudate/putamen (dorsal striatum) that originates from the substantia nigra pars compacta (SNc) facilitates an organism’s behavioral reactivity to sensory stimuli primarily of isocortical origin. For the mesolimbic system, DA input to the nucleus accumbens (NA = ventral striatum) that originates from the ventral tegmental area (VTA) facilitates an organism’s behavioral reactivity to sensory stimuli derived from the amygdala (Amyg), hippocampus (Hipp), and allocortical parts of the prefrontal cortex (PFC). Modified from Figure 1.3 in Numan and Stolzenberg [713] with permission from Elsevier.

[310,331,361,434]. Sensory association isocortex projects to the caudate and putamen, or dorsal striatum, and uses glutamate as an excitatory neurotransmitter. The main projection or output neurons of the dorsal striatum are the GABAergic medium spiny neurons (MSNs), and their efferents form two major output pathways: the direct pathway, whose activity facilitates movement, and the indirect pathway, whose output suppresses movement. The MSNs of the direct pathway contain the D1 class of DA receptors, while the MSNs of the indirect pathway contain the D2 class of DA receptors. MSNs have high K⁺ permeability, and their resting membrane potential is very negative, near the K⁺ equilibrium potential of about −80 mV. Therefore, it is hard for excitatory cortical input to activate these neurons to the threshold for action potentials, and they are typically viewed as being in a downstate or hyperpolarized. When DA input from the SNc acts on D1 receptors on the MSNs of the direct pathway, in conjunction with excitatory cortical input, it acts to facilitate the depolarization of the MSNs of the direct pathway, bringing them to an upstate of about −65 mV. This upstate makes the MSNs more easily activated by strong sensory inputs from the isocortex. Once the direct pathway is activated, the GABAergic MSNs inhibit the internal segment (medial) of the globus pallidus (GPi). Since the GABAergic output of GPe inhibits the brainstem motor area and the ventrolateral thalamic nucleus (VL), two brain regions whose efferents facilitate movement, activation of the direct pathway stimulates movement through a process of disinhibition (inhibition is removed from BSMA and VL).

With respect to the indirect pathway, very strong cortical input can bring these MSNs into the upstate and activate them. These MSNs project to and inhibit the GABA output neurons of the external segment of the GP (GPe). When active, GPe functions to inhibit the subthalamic nucleus (STN). STN is also excited by glutamatergic afferents from the isocortex. Therefore, activation of the indirect pathway stimulates the STN through disinhibition, which potentiates the effects of isocortical stimulation of STN. Excitatory glutamatergic neurons of the STN activate GPi, which results in movement inhibition (because BSMA and VL are inhibited). This would be a mechanism that would allow cortical mechanisms to terminate a movement or depress unwanted movements. Importantly, DA action on D2-like receptors in the dorsal striatum depresses the ability of the isocortex to activate the MSNs that contribute to the
indirect pathway. Therefore, activity within the nigrostriatal DA pathway and DA action on both D1 and D2 receptors facilitates movement by suppressing the indirect pathway and facilitating the direct pathway. One can therefore describe the following motor mechanism in the dorsal basal ganglia: when the cortex orders a movement, in conjunction with DA release, the direct pathway is activated and the indirect pathway is inhibited. To terminate the movement, DA levels decline, and the indirect pathway is activated by strong cortical input.

There is recent experimental evidence that has offered excellent support for the operational characteristics of the dorsal basal ganglia as described above [411,509]. For example, in mice, optogenetic stimulation restricted to MSNs of the direct pathway (that contain D1 receptors) has been shown to facilitate movement, while optogenetic stimulation of D2 receptor containing MSNs (which would be inhibited by dopamine (DA)) depresses locomotion (see Box 1.1).

**1.3.4.3 Operation of the Mesolimbic Dopamine System and the Ventral Basal Ganglia**

The operation of the mesolimbic DA system is less well understood [434,881,914]. The ventral striatum, which contains the nucleus...
accumbens (NA), receives excitatory glutamatergic inputs from the basolateral and basomedial amygdala, hippocampus, and prefrontal cortex, and DA input from the VTA. NA has been divided into a medial or shell part (NAS) and a lateral or core part (NAc). Individual GABAergic MSNs in NA core and shell, which for the most part contain either D1 or D2 receptors, project to a variety of target regions, including a dominant projection to the ventral pallidum (VP), which forms the NA-VP circuit [575,815,974,984,1075]. It is not yet entirely clear, however, whether distinct direct and indirect pathways emanate from NA, with activity in a putative direct pathway promoting goal-directed behaviors, and activity in a putative indirect pathway inhibiting such behaviors. It is also not clear whether DA acts on D1 receptors to stimulate a direct pathway and on D2 receptors to suppress an indirect pathway.

Figure 1.9 shows a simplified schematic of the ventral basal ganglia. Both D1 receptor containing and D2 receptor containing NA MSNs project to VP [434,575,815,914,1075], and VP targets include the subthalamic nucleus, brainstem motor areas, and mediodorsal thalamus (MDT) [362]. Drawing an analogy from the dorsal basal ganglia, one could argue that VP presents a mixture of both the external and internal segments of the globus pallidus, with VP projections to BSMA and MDT representing aspects of the direct pathway, while VP projections to STN would be a component of the indirect pathway. However, to my knowledge, it has not been shown that NA D2-containing MSNs only project to those parts of VP that project to STN while NA D1-containing MSNs only project to those parts of the VP that project to either BSMA or MDT. It is also not known whether STN stimulates those VP neurons that project to BSMA and MDT. Finally, while the predominant output neurons of the globus pallidus are GABAergic, exerting an inhibition over their targets (see Figure 1.8), the VP output neurons are not only GABAergic but also contain a significant population of excitatory glutamatergic projection neurons [328].

With respect to the operation of the NA-VP circuit, the seminal research of Mogenson...
led to the proposal that the activity of GABAergic NA MSNs restrains goal-directed motivated behavior, and that the function of DA action on NA was to depress the output of these MSNs, in this way disinhibiting VP, the activity of which was considered to promote goal-directed behavior. There is a substantial amount of current research that supports this view [696,803,805,876,915,956,1042]. In opposition, however, there is also a literature that supports the view that DA action on NA stimulates GABAergic MSN output, which might then inhibit target regions such as VP, and that such actions activate goal-directed behavior [24,411,562,939]. These two bodies of research could be conceived as being consistent with the existence of both an indirect and direct pathway, respectively, emanating from NA.

In an interesting study by Wirtshafter and Stratford [1040], rats were trained on a progressive ratio 6 (PR6) schedule of reinforcement using food as a reward. On this schedule, the first response on the operant lever is rewarded, but then the number of responses required to earn each subsequent food pellet is increased by six after each reinforcement, so that seven responses are required for the second reward, 13 for the third, and so on. The break point is defined as the number of lever presses the rat makes for a reward before it ceases responding for 3 min. The idea here is that a higher break point indicates greater motivation or greater goal-directed behavior. In animals that received saline injections into NAs, the break point was about 60 operant responses. When amphetamine was injected into NAs, which would increase DA release and increase activation of both D1 and D2 receptors, the average break point increased to about 80 bar presses. Most importantly, the injection of muscimol into NAs also increased the break point to about 80. This last result suggests that a global inhibition of NAs activity, without any activation of a supposed direct pathway, can increase motivation or goal-directed approach responses to rewarding stimuli. To the extent that the NAs GABAergic MSNs were inhibited, this should cause increased activity in VP. Therefore, increased VP activity may have increased the break point in the Wirtshafter and Stratford study. In support, Farrar et al. [284] reported that rats with VP inactivation had diminished willingness to work hard on an operant conditioning task to obtain sucrose reward.

In order to resolve these controversies, perhaps different functional populations of neurons exist within the NA-VP circuit [752]. Not only may NAs be distinct in function from NAc [71,434], but subcircuits within each of these broad NA regions may also have distinct input–output relations that have different operational rules. These different populations may regulate separate and distinct larger neural networks; for certain goal-directed behaviors, it might be important for DA action on NA to primarily suppress NA and disinhibit VP, while for other behaviors, the reverse might be the case [127].

### 1.3.4.4 The Numan Model

I have presented a neural model of ventral basal ganglia function [696,713,714] based on the early ideas of Mogenson [655] and my research on maternal behavior, which will be described in Chapter 5. Aspects of this model are shown in Figure 1.10(A) and may be most accurate with respect to the operation of only certain circuits within NAs. The model shows the basal amygdala (BLA/BMA) providing excitatory sensory inputs to both the NA and VP [757,760]. The output of VP is conceived as being essential for goal-directed responses. Without DA release into NA, the functional effects of BLA/BMA projections to NA and VP cancel each other out. This happens because BLA/BMA activation of NA causes GABA release into VP, which blunts the VP response to its inputs. However, when DA is released into NA, the model proposes that DA acts to suppress the response of NA to input from the amygdala; therefore, less GABA is released.
into VP, which opens a gate allowing VP to respond to BLA/BMA inputs and promote goal-directed responses. Counter intuitively (based on the operation of the dorsal basal ganglia), my model actually proposes that such DA inhibition of NA responsiveness is caused by DA action of D1 receptors. Therefore, this model does not include a supposed direct pathway, where enhanced NA output would be essential for goal-directed maternal responses.

Since a large body of data on the dorsal basal ganglia suggests that DA action on D1 receptors stimulates MSN output from the dorsal striatum, how could DA action on D1 receptors restrain NA MSN output to VP? Unlike the dorsal striatum, there is a significant population of D1 receptors that are located on the axon terminals of glutamatergic afferents to NA [260]. This anatomical relationship is shown in Figure 1.10(B). Importantly, DA action on presynaptic D1 receptors results in presynaptic inhibition of glutamate release, which would depress NA MSN activation by incoming afferents [177, 260].

This analysis indicates that the organization of the ventral basal ganglia is complex and that different types of motivated behaviors may be regulated in different ways by this system. Therefore, for a general statement, it might be best to propose that DA action on the NA-VP circuit promotes goal-directed behaviors.

1.3.4.5 The Role of the Hypothalamus in VTA-DA Activation

What causes DA to be released into NA so it can act on D1 and D2 receptors? Given the role of the hypothalamus in motivation, it makes sense that it is one of the sources of mesolimbic DA activation [716]. The hypothalamus is conceived as monitoring an organism’s internal state while also being responsive to the external environment. When appropriate, the hypothalamus would activate DA release into NA through its known projections to the

![Figure 1.10](image_url)
VTA [328] in order to promote adaptive goal-directed responses. Different hypothalamic nuclei, related to different motivational states [950], might be responsive to specific aspects of an organism’s internal environment and to specific external stimuli. Under the right conditions, such nuclei might activate the mesolimbic DA system. Let’s take two examples (see [716]): goal directed food-seeking responses and goal-directed maternal responses. For food intake or hunger, the lateral hypothalamus (LH; a region that regulates food intake) may respond either directly or indirectly to glucose or fat levels. When energy supplies are low due to a period without food intake, stimuli that have previously been associated with food, or distal food stimuli, may become capable of activating LH, which then stimulates VTA to promote food-seeking behavior. Once food is obtained, LH projections to the brainstem and spinal cord may regulate consummatory responses. In the absence of food deprivation, the LH would not be responsive to food-related stimuli, and food seeking and eating would not occur at a high level. With respect to maternal behavior, pregnancy hormone action on the medial preoptic area (MPOA; a hypothalamic region that regulates maternal responsiveness; see Chapter 5) may render the MPOA responsive to infant-related stimuli; MPOA projections to the mesolimbic DA system would then facilitate maternal infant-seeking behaviors so a mother would be able to contact her infants. MPOA projections to the brainstem and spinal cord may regulate consummatory nursing behavior, once the mother has gained contact with her infants (see Figure 1.3). For each of these cases, specific goal-directed responses are the result of specific hypothalamic neurons, with unique functions, activating DA release into NA, with the result that the NA-VP circuit becomes responsive to stimuli associated with a specific motivational state.

This analysis indicates that the hypothalamus is positioned to play an important role in the regulation of the specificity of goal-directed motivation. The mesolimbic DA system and the NA–VP circuit can be conceived as a nonspecific motivational system in the sense that DA release into NA regulates a variety of goal-directed behaviors [272,716]. However, just which goal-directed response occurs depends on whether DA is released into NA in the presence of particular stimuli. Given that different nuclei in the hypothalamus appear to be involved in specific motivational processes, as described above (also see [950]), hypothalamic output to VTA-DA neurons may direct the types of goal-directed responses that occur. In other words, hypothalamic connectivity with the mesolimbic DA system may mediate an interaction between specific and nonspecific motivational systems, with the hypothalamus influencing the particular stimuli that are processed by the NA-VP at any one point in time.

With respect to the idea that the hypothalamus may activate VTA-DA neurons, a neuroanatomical study by Geisler et al. [328], which combined the injection of a retrograde tracer into the VTA with detection of mRNA for the vesicular glutamate transporter in neuronal cell bodies, found that several hypothalamic nuclei provided glutamatergic (excitatory) inputs to VTA. These nuclei included: MPOA, LPOA, LH, and VMN. Although the AHN did not have a major projection to VTA, the AHN does project to PAG, which in turn has a glutamatergic projection to VTA. Although this research supports the idea that the hypothalamus may stimulate the mesolimbic DA system, this study did not examine the VTA neuron type that received the glutamatergic inputs. In addition to DA neurons, the VTA also contains GABA and glutamate neurons [724,1047].
Other research, however, indicates that glutamatergic input to VTA is a major stimulator of VTA-DA neurons [881,1078].

**1.3.4.6 The Mesolimbic DA System and Goal-Directed Approach and Avoidance Responses**

In line with the examples that have been presented, most investigators view the mesolimbic DA system as a reward pathway [881]—DA release into NA affects the way the NA-VP circuit responds to appetitive or reward-related stimuli, leading to goal-directed reward-seeking behaviors. This view, of course, is the one taken by Ernst and Fudge [272]. Research has clearly shown that DA release into NA promotes food-seeking behaviors and the appetitive aspects of sexual and maternal behaviors [50,716,904,929]. This reward view of mesolimbic DA function is shown in Figure 1.11.

Although the neural model of Ernst and Fudge [272] labels the amygdala as primarily involved in avoidance and the ventral striatum as involved in approach, a conflict arises because the operation of the mesolimbic DA system in the context of appetitive (approach) motivation is based in part on the neural inputs that the NA-VP circuit receives from amygdala neurons with a positive valence. For example, Simmons and Neill [904] found that when muscimol was injected into the BLA on one side of the brain and a DA receptor antagonist was injected into the nucleus accumbens on the opposite side of the brain, a rat’s operant responding for a food reward was significantly suppressed. This finding and the logic behind it can also be used to question the exclusive role of the mesolimbic DA system in reward; since BLA also contains neurons that respond to aversive stimuli, couldn’t BLA input to NA-VP also play a role in goal-directed avoidance behaviors, and couldn’t the effects of such input be potentiated by DA?

Therefore, a broader view of the functional role of the mesolimbic DA system is based on the facts that individual BLA/BMA neurons respond to stimuli with either a positive or a negative valence and that BLA/BMA projects to NA-VP circuit. From this perspective, DA release into NA should be able to affect subcircuits in NA-VP that are engaged by either appetitive or aversive stimuli. When DA is released into NA in the context of appetitive stimuli, reward-seeking behaviors occur, but when DA is released into NA in the context of aversive stimuli, goal-directed avoidance or rejection responses occur. This view is based on the idea that the limbic motor system is not likely to regulate only positive approach responses. Would one assume that the “cognitive motor system”, that is, nigrostriatal DA regulation of the dorsal basal ganglia, only affected moving forward or to the right but not backwards or to the left?

A neural model that incorporates ideas about how the mesolimbic DA system might work is shown in Figure 1.12. This model, which focuses on BLA/BMA input to NA-VP, takes a

![Figure 1.11](image-url)
1.3 Functional Neuroanatomy

FIGURE 1.12 Distinct neural circuits within the mesolimbic dopamine (DA) system that regulate either reward-seeking responses to appetitive stimuli or active avoidance/rejection responses to aversive stimuli. Basolateral amygdala (BLA) and basomedial amygdala (BMA) contain separate neurons that respond to either appetitive or aversive stimuli. These neurons are labeled with a positive or negative sign, respectively. These positive or negative inputs are then relayed to distinct neurons within the nucleus accumbens-ventral pallidum circuit (NA-VP), the outputs of which give rise to either goal-directed approach or avoidance/rejection responses, respectively. DA input to these NA-VP circuits can potentiate either goal-directed appetitive or avoidance/rejection responses, depending on the particular circuits that are active. The hypothalamus (along with other areas) provides stimulatory inputs to ventral tegmental area (VTA) DA neurons.

labeled-line point of view where positively or negatively valent neurons in the limbic system project to distinct parts of the NA-VP circuit in order to regulate either goal-directed appetitive responses or goal-directed avoidance responses. This view argues that noxious or aversive stimuli, like reward-related stimuli, should activate DA release into NA. Anatomically, it has already been suggested that hypothalamic projections to VTA may be one of the neural inputs that activate DA release into NA. Since the hypothalamus contains neurons involved in defensive, avoidance, and aggressive behaviors, as well as appetitive behaviors, it should be possible for the hypothalamus to be involved in activating DA release into NA in situations involving either approach or avoidance.

Some evidence that supports the model shown in Figure 1.12 is described below.

1. Neurophysiological research indicates that different VTA-DA neurons can be activated by either appetitive or aversive stimuli, respectively [126,130,612]. Although some avoidance responses may be regulated by VTA projections to regions outside the NA-VP circuit [526], I want to focus on the research that supports the view that VTA-DA projections to NA-VP can influence both goal-directed appetitive and aversive responses. Most of the research described below focuses on the role of the mesolimbic DA system in goal-directed avoidance and rejection, since the role of this system in reward seeking has already been reviewed.

2. Anstrom, Miczek, and Budygin [33] reported that in aggressive encounters between a resident rat and an intruder, when the intruder is being defeated and shows defensive and submissive postures, DA is released into NA and action potential frequency concomitantly increases in the VTA. These results indicate that aversive social conditions, not obviously linked to rewarding stimuli, are associated with DA release into NA. Similarly, Badrinarayan et al. [46] have reported that the presentation of a conditioned aversive stimulus (a CS that had been paired with shock) activated DA release into NAs.

3. McCullough, Sokolowski, and Salamone [620] have shown that DA input to NA is necessary for the performance of an instrumental active avoidance response.
In the instrumental task lasting 45 min, a shock was presented to rats for 5 s every 30 s, but the rats could escape or avoid the shock for 30 s by pressing a lever. Performance on the avoidance task (in well-trained rats) led to significant increases in extracellular DA levels, as measured by microdialysis. There was a significant positive correlation (0.78) between DA increases and number of avoidance responses. In a second experiment, groups of rats were trained on the lever press avoidance procedure. After training, rats received intra-accumbens injections of 6-hydroxydopamine (6-HD) or vehicle. The 6-HD is a dopaminergic neurotoxin that destroys DA neurons and therefore would destroy DA axon terminals in NA. Dopamine depletion in NA led to a substantial decrease in lever pressing to avoid or escape shock. However, these rats did not appear to lose sensitivity to shock, as they were seen to flinch or vocalize with shock presentation. In contrast to controls, DA-depleted rats were all observed to freeze or become immobile during shocks, while controls, if they did not avoid, would engage in active instrumental lever pressing escape responses. It is interesting to speculate that as a result of DA depletion, rats showed consummatory reflexive defensive responses to shock but were not able to show goal-directed avoidance responses.

In line with these early results [620], additional recent work supports the view that DA action in NA is essential for goal-directed avoidance responses [215,1034]. Further, fMRI research on humans has reported an increased NA blood-oxygen-level dependent (BOLD) response, presumably due to enhanced DA release into NA [872], during the performance of an active avoidance response where a button press after a warning signal prevented the appearance of an aversive visual image [547].

In the amygdala section, evidence was presented that BLA/BMA is involved in active avoidance responding. Given that BLA/BMA projects to the NA-VP circuit, the above results fit with the model shown in Figure 1.12 with respect to goal-directed avoidance.

4. Research from Berridge’s group has presented important results that show that there is a topographic organization of NA function with respect to appetitive and aversive motivation [285,803,805]. They showed that inhibition of neural activity in the rostral NAs, with either muscimol or a glutamate receptor (GluR) antagonist, promoted appetitive motivation, while inhibition of neural activity in the caudal NAs promoted aversive motivation. Importantly, DA action on D1 receptors in the rostral NAs was necessary for the promotion of appetitive behavior by GluR antagonist-induced inactivation of rostral NAs, while DA action on both D1 and D2 receptors in the caudal NAs was necessary for the potentiation of aversive motivation by GluR antagonist-induced inactivation of caudal NAs. One way to interpret these results is that DA action in NAs facilitates the effects of NAs inactivation on motivated behaviors. These results are important because they show that suppression of NA output, which presumably releases VP from inhibition, can promote either approach or avoidance responses depending on the particular neural circuits that are affected, and that DA action on NA is involved in both of these motivational effects.

1.3.5 The Prefrontal Cortex

1.3.5.1 Introduction

Ernst and Fudge [272] proposed that the prefrontal cortex (PFC) serves to modulate or regulate the output of the amygdala and ventral striatum so that adaptive and appropriate
goal-directed responses occur. Given the strong neural inputs that the PFC receives from sensory association neocortex [61], one might view the PFC as exerting executive, rational, or cognitive control over basic goal-directed approach and avoidance responses. Many researchers view PFC control mechanisms as downregulating or restraining basic aversive and appetitive responses controlled by the amygdala and the NA-VP circuit [397], in this way dampening overly fearful or aggressive responses to potential threats and risky appetitive responses to rewarding stimuli. Since cortical projection neurons are glutamatergic, any inhibitory effects that the PFC might have on either amygdala or ventral striatum output would have to be mediated by projections to inhibitory interneurons. In addition to this perspective of a PFC restraining influence, evidence will be presented that PFC connections to the amygdala and NA-VP circuit can also enhance aversive and appetitive responses. In other words, the PFC is positioned to downregulate or upregulate amygdala and NA-VP output, depending on the particular PFC neurons that are exerting such modulatory actions.

To offer an illuminating proposal with respect to human social behavior, political and religious ideologies often construct our social world into in-groups and out-groups. To the extent that the socialization processes through which ideologies are learned are incorporated within the isocortex and PFC, then one might assume that PFC output to the amygdala and NA-VP circuit would enhance social avoidance and rejection responses to out-group members, depress such responses to in-group members, and enhance acceptance responses to one’s in-group members (see [698] and Chapter 7).

The anatomy of the PFC is complex, and I will only present a brief overview for primates and rats [60,61,210,319,320,726,786,787,799]. In primates, the PFC can be divided into three major regions: lateral PFC, orbital PFC, and medial PFC. The lateral PFC and some parts of the medial and orbital PFC are isocortex, while the remaining parts of the medial and orbital PFC are allocortical in nature and a well-developed granular layer 4 is not present. In rats, all major parts of the PFC are allocortical and agranular (lacking a layer 4). Although rats do not have an isocortex equivalent to the lateral PFC, it has been suggested that an area referred as the precentral cortex (the area rostral to the primary motor cortex, also referred to as the frontal pole area), may represent a rudimentary granular (isocortical) PFC [787]. Because of species differences in the cytoarchitecture of the PFC, a current definition that is applicable across species is that the PFC is composed of those parts of the cortex in the lateral, orbital, and medial frontolobe that are rostral to the primary motor cortex and that also receive significant neural inputs from the mediodorsal thalamic nucleus (MDT; [726]). As an example, since the anterior part of the cingulate cortex (ACC) receives significant input from MDT, it has been included as part of the medial prefrontal cortex in both rats and primates.

Figure 1.13 shows a schematic of the lateral, orbital, and medial PFC in primates. Based on cytoarchitectonic differences between PFC regions, different areas have been assigned different numbers in order to differentiate the regions. Only some of these area numbers are shown in the figure. The orbital PFC can be divided into medial, central, and lateral parts. Important regions in the medial PFC include area 24 (dorsal ACC), area 25 (ventral or subgenual ACC), and area 32 (the medial PFC region rostral to areas 24 and 25). All of these medial PFC regions are allocortical in nature, and it is these particular medial PFC regions that will be emphasized throughout this book because homologous areas also exist in rodents, which will permit an integration of human and animal studies with respect to medial PFC function. Figure 1.14 shows a frontal section through the rat brain that defines the various regions of the PFC. As indicated, the precentral cortex (PrC) of the rat PFC may be homologous
to the primate lateral PFC. With respect to the
rat medial PFC, the ACC, prelimbic cortex (PL),
and infralimbic cortex (IL) are considered to
be homologous to primate areas 24, 32, and 25,
respectively [320,787]. As in primates, the rat
orbital regions can also be divided into medial
(medial and ventral orbital), central (ventrolat-
eral orbital), and lateral orbital (LO) cortices, and
the anterior insular cortex (AI). The precentral cortex (PrC)
may be homologous to the primate lateral prefrontal cortex.
Also shown are the anterior olfactory nucleus (AON), the
primary motor cortex (PMC), and corpus callosum (CC).
Modified from Figure 1(b) in Dalley et al. [210], with permission
from Elsevier.

FIGURE 1.13 Lateral, mid-sagittal, and ventral views
of the primate brain, emphasizing the locations of different
parts of the prefrontal cortex. The lateral prefrontal cortex
(LPFC) is shown in the frontal lobe rostral to the primary
motor cortex (PMC). The mid-sagittal section shows three
important areas within the medial prefrontal cortex, labeled
as areas 24, 25, and 32. These areas are located in the ante-
rior parts of the cingulate cortex (CG=cingulate gyrus). The
orbital prefrontal cortex is shown in the ventral view, and
contains the medial (MO), central orbital (CO), and lateral
orbital (LO) regions. Other abbreviations: CC=corpus cal-
losum; HYP=hypothalamus; LF=lateral fissure; OB=olfac-
tory bulb; OC=occipital lobe; PSS=primary somatic sensory
cortex; TL=temporal lobe. Modified from Figure 2.8 in Fuster
[319], with permission from Elsevier.

FIGURE 1.14 A frontal section showing the major parts
of the rat prefrontal cortex. These parts include the anterior
cingulate cortex (ACC), prelimbic cortex (PL), infralimbic
cortex (IL), medial orbital (MO), ventral orbital (VO), ven-
trolateral orbital (VLO), and lateral orbital (LO) cortices, and
the anterior insular cortex (AI). The precentral cortex (PrC)
may be homologous to the primate lateral prefrontal cortex.
Also shown are the anterior olfactory nucleus (AON), the
primary motor cortex (PMC), and corpus callosum (CC).
Modified from Figure 1(b) in Dalley et al. [210], with permission
from Elsevier.
Based on neuroanatomical connectivity, Price [787] and Ongur and Price [726] have divided parts of the PFC into a medial network and an orbital network. To simplify, the medial network consists of the medial PFC and most medial orbital PFC regions, while the orbital network is composed of most parts of the central and lateral orbital PFC. Table 1.1 provides a summary of the PFC areas in the primate and rat and their likely homologies. A block diagram of some of the important neural connections within the prefrontal cortex is shown in Figure 1.15 [61,320,622,726,786,787,799]. The lateral PFC and the orbital network are the main recipients of processed sensory inputs from the sensory association cortex. Sensory inputs can reach the medial network via its connections with the orbital network and with the entorhinal cortex. Finally, both the medial and orbital networks have reciprocal connections with the amygdala, while the medial network provides the major efferent pathways to the ventral striatum (NA) and to the hypothalamus.

In viewing this organization, one can conceive of how the reciprocal interactions between the lateral PFC and sensory association cortex, along with the connections of the lateral PFC with the primary motor cortex, may be involved in working memory, attentional processes, and movement planning [61], while the connections of the lateral PFC-sensory association complex with the orbital and medial networks would allow cognitive processes to regulate neural activity within the amygdala, striatum, and hypothalamus. This latter circuit mechanism would allow a sort of hierarchical top-down regulation, where neocortical cognitive processes influence allocortical and subcortical neural events.

The projections from the amygdala to the PFC are also worth considering. Barbas et al. [61] have emphasized the connection between the basal nuclei of the amygdala with the posterior orbital PFC. The amygdala not only projects directly to the PFC but also indirectly via connections with MDT. They compare the amygdala-to-MDT-to-orbital PFC connection with those of the major sensory systems, such as vision, where the optic tract projects to the lateral geniculate nucleus, which in turn projects to the primary visual neocortex. This comparison suggested to them that the relay of amygdala input to the posterior orbital PFC via the MDT might be the route through which emotions are subjectively experienced. Amygdala projections to the anterior insular cortex also seem to be important in this regard.

With respect to involvement of such amygdala-orbital PFC connections in emotional experience, a disruption in such pathways may explain why SM is unable to experience fear. Interestingly, a recent study [288] has reported that SM and two other patients with amygdala lesions caused by Urbach–Wiethe disease can experience fear under certain conditions. The inhalation of CO₂, which caused an oxygen deficit, evoked fear and panic attacks in these patients. Therefore, the amygdala-to-orbital PFC connection may be important for the experience of fear that is induced by exteroceptive aversive

### Table 1.1 Comparisons of Some of the Prefrontal Cortical Regions in Primates and Rodents

<table>
<thead>
<tr>
<th>Primates</th>
<th>Rodents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEDIAL NETWORK</strong></td>
<td></td>
</tr>
<tr>
<td>Area 24 (dorsal ACC)</td>
<td>ACC</td>
</tr>
<tr>
<td>Area 32</td>
<td>PL</td>
</tr>
<tr>
<td>Area 25 (subgenual ACC)</td>
<td>IL</td>
</tr>
<tr>
<td>Medial orbital</td>
<td>MO/VO</td>
</tr>
<tr>
<td><strong>ORBITAL NETWORK</strong></td>
<td></td>
</tr>
<tr>
<td>Central orbital</td>
<td>VLO</td>
</tr>
<tr>
<td>Lateral orbital</td>
<td>LO/AI</td>
</tr>
<tr>
<td><strong>OTHER AREAS</strong></td>
<td></td>
</tr>
<tr>
<td>Lateral PFC</td>
<td>PrC</td>
</tr>
</tbody>
</table>

Abbreviations: ACC = anterior cingulate cortex; AI = anterior insular cortex; IL = infralimbic cortex; LO = lateral orbital cortex; MO = medial orbital cortex; PFC = prefrontal cortex; PL = prelimbic cortex; PrC = precentral cortex; VLO = ventrolateral orbital cortex; VO = ventral orbital cortex.
stimuli, while interoceptive visceral (autonomic) stimuli that evoke fearfulness appear to reach the orbital PFC (or other brain regions) through circuits that do not require the amygdala.

For a final consideration, the facts that the amygdala projects to the medial and orbital networks, and that the medial network projects to lateral PFC, also suggest routes over which the valence characteristics of stimuli processed through the amygdala (emotional and motivational processes) might influence cognitive processes and decision making within the lateral prefrontal-sensory association cortex complex.

In order to fully appreciate the interactions of the prefrontal cortex with the amygdala and ventral striatum in the control of motivational and emotional processes, a more detailed evaluation of the particular nuclei and microcircuitry involved is necessary. I will present several examples from rodents and primates to help elucidate such interactions, and I will start with simpler processes to show how PFC output to the amygdala can either decrease or increase CFRe.s that result from amygdala projections to the brainstem. The important role of PFC interactions with the hypothalamus will not be discussed in detail in this chapter but will be fully discussed in subsequent chapters.

### 1.3.5.2 PFC Regulation of Conditioned Fear Responses and Goal-Directed Responses

In reference to Figure 1.6, recall that the CFR occurs when a neutral CS, such as a tone, is paired with an aversive US (shock). The neural circuitry analysis presented showed that CS–US pairings strengthened the ability of the CS to activate an LA-to-BLA-to-CeAm-to-PAG circuit. Recent research has shown that the output of the medial PFC can modulate this amygdala-based CFR. In fact, different regions of the medial PFC have been shown to have opposing effects—the output of IL area exerts an inhibitory effect on the CFR while the output of the PL area has a potentiating effect [645]. The effects of the medial PFC on the CFR have often been studied in the context of extinction learning [995]. Fear extinction describes the decrease in the CFR that occurs after repeated presentations of the CS without the US. The experiments by Vidal-Gonzalez et al. [995] used the following paradigm. First, rats were conditioned: a tone...
CS was presented for 30 s and was coterminated with a 1 s shock. The CFR was measured by the percentage of time the rats were immobile during the 30 s CS interval. Once the criterion for CFR acquisition was achieved (>20% immobility), on the following day, rats were exposed to partial extinction training composed of eight tone presentations without shock. During tone presentation, rats received microstimulation of PL cortex or IL cortex, or were unstimulated. IL stimulation enhanced extinction, and PL stimulation delayed extinction. Based on other neuroanatomical and neurophysiological data, the microcircuitry shown in Figure 1.16 has been proposed to explain these results [20, 69, 645, 995]. PL stimulation may enhance the CFR by activating BLA neurons that are part of an aversive BLA-to-CeAm-to-PAG circuit, while IL stimulation may depress the CFR by activating inhibitory ITC interneurons or the inhibitory neurons in CeAl, both of which would depress the output of CeAm projections to PAG.

Similar processes may also occur in primates as recent work indicates that inactivation of parts of the medial PFC in monkeys, which may be homologous to the rodent PL cortex, potentiated the long-term extinction of a CFR [496].

The involvement of the IL PFC in suppressing Pavlovian CFRs may also occur in humans. Using fMRI studies, it has been shown that as extinction learning proceeds, increases in the BOLD signal in the subgenual ACC (area 25, the presumed homolog of IL cortex) is correlated with BOLD decreases in the amygdala [394]. These authors have also reviewed the evidence that posttraumatic stress disorder, where patients exhibit a cue activated reexperience of a traumatic event when the cue no longer signals danger, may be related to a dysfunction of ventromedial PFC regulation of amygdala activity.

This research on different divisions of the medial PFC exerting opposing influences on fear-related consummatory processes may also be related to the therapeutic effectiveness of deep brain stimulation (DBS) for treating certain forms of clinical depression in human patients [421]. DBS of areas 32 (homologous to PL cortex) and 25 (homologous to IL cortex) has been associated with decreases in depressive symptoms [379]. Although it is usually argued that DBS is effective because it exerts inhibitory effects, there is also evidence that it might stimulate neural tissue near the site of the electrode [379]. Since some forms of severe depression are associated with intense anxiety states and since stress reactivity and fearfulness may be precipitating factors for depression [703], it is interesting to speculate that DBS may be therapeutic because

FIGURE 1.16 Medial prefrontal cortex projections to the amygdala can either upregulate or downregulate the conditioned fear response (CFR). Amygdala neurons that respond to aversive, negatively valent stimuli are shown with a negative sign within their cell bodies. The classic CFR circuit (LA-BLA-CeAm) is shown as projecting to the periaqueductal gray (PAG) to cause the conditioned freezing response. The rat prelimbic cortex (PL), which may be homologous to area 32 in primates, is shown as promoting the CFR by stimulating BLA projections to CeAm. The infralimbic cortex (IL), which may be homologous to area 25 in primates, is shown as depressing the CFR via excitatory projections to CeAl and ITC. (IL may also suppress the fear response by projecting to those BLA neurons that stimulate CeAl and ITC: see Figure 1.6(A)) Axons ending in a bar are inhibitory, and those ending in an arrow are excitory. Other abbreviations: BLA = basolateral amygdala; CeAl = lateral part of the central nucleus of the amygdala; CeAm = medial part of the central nucleus of the amygdala; CS = conditioned stimulus; ITC = intercalated nuclei; LA = lateral amygdala.
it is ultimately modifying amygdala reactivity to stress and anxiety-inducing stimuli.

The importance of all of these findings is that they show that different neurons within the medial PFC cortex, through differential projections to the amygdala, can either increase or decrease the ability of stimuli to activate reflex-like conditioned fearfulness. Such findings open up the possibility that PFC projections to the amygdala might also be capable of downregulating or upregulating goal-directed avoidance or appetitive responses, depending on whether PFC neurons inhibit or activate positive or negative BLA neurons that project to the NA-VP circuit. How might the PFC be involved in promoting goal-directed avoidance responses? One possibility is that particular medial PFC efferents to the amygdala may depress the CFR to aversive stimuli so that the animal does not become immobile, while other PFC efferents act to facilitate goal-directed active avoidance responses to aversive stimuli by potentiating negatively valent amygdala neuron input to the NA-VP. Recent evidence has presented some support for such possibilities in rats [667], and hypothetical neural circuits mediating such effects are shown in Figure 1.17(A). Such an analysis suggests that PFC inputs to the amygdala may be involved in adaptive coping responses by inhibiting reflexive fear responses while promoting proactive responses that avoid primary aversive stimuli.

A recent report by Amemori and Graybiel [25] is also relevant to the role of the medial PFC in the modulation of goal-directed responses.

FIGURE 1.17  (A) Prefrontal cortex (PFC) connections with the amygdala can suppress the conditioned fear response (CFR) and facilitate the conditioned avoidance response (CAR) to an aversive stimulus by inhibiting CeAm output to the periaqueductal gray (PAG), while facilitating BLA projections to the nucleus accumbens-ventral pallidum circuit (NA-VP). Compare to Figure 1.6(B). Amygdala neurons that respond to aversive stimuli have a negative sign within their cell bodies. Other abbreviations: BLA = basolateral amygdala; CeAl = lateral part of the central nucleus of the amygdala; CeAm = medial part of the central nucleus of the amygdala. (B) Medial prefrontal cortex (mPFC) projections to the nucleus accumbens (NA) can either stimulate or depress medium spiny neuron (MSN) projections to the ventral pallidum (VP), depending on the particular neural circuits that are active. For both parts of this figure, axons ending in a bar are inhibitory, and those ending in an arrow are excitatory.
Rhesus monkeys were trained on an operant approach-avoidance task. A visual stimulus, composed of a yellow bar and a red bar, was presented on a screen. The lengths of the red and yellow bars corresponded to the amount of liquid food and the strength of an air puff, respectively, that the monkey would receive if it performed an approach response. If the monkey performed an avoidance response, it did not receive food or an air puff. An approach response consisted of moving a joystick in the direction of a plus sign, while an avoidance response consisted of moving the joystick in the direction of a square. Obviously, if the visual cue indicated a large food reward and a small air puff, the monkey would make an approach response, while if the predicted outcome was a small food reward and a strong air puff, an avoidance response would be appropriate. These response decisions, of course, were not absolute, but instead occurred across a continuum, so that as the relative sizes of the predicted food reward decreased and the air puff strength increased, the probability of approach responses to the visual signal decreased and the probability of an avoidance response increased. In one part of this study, the authors recorded from neurons in the dorsal anterior cingulate cortex, which is part of the primate medial PFC. Neurons could be categorized into two main types. For one group of neurons, increased neural spiking was correlated with approach responses, while neural activity in the other group was correlated with avoidance responses. Interestingly, in the dorsal parts of the dorsal ACC, these two types of neurons were intermixed, but in the ventral part of the dorsal ACC, which might be homologous to the rat’s PL cortex, a predominance of avoidance neurons were detected. Significantly, microstimulation of this ventral part of the dorsal anterior cingulate region biased the monkeys’ responses in the direction of goal-directed avoidance, which could be taken to indicate that such stimulation increased fearfulness, anxiety, or the ability of particular visual signals to stimulate amygdala circuits that promoted goal-directed avoidance responses.

The Amemori and Graybiel [25] study did not examine the brain regions that received inputs from the dorsal ACC. Since the medial PFC projects to both the ventral striatum and the amygdala, goal-directed responses regulated by the medial PFC could include influences on either the amygdala, striatum, or both regions. In this context, I want to present the results of another study that showed that medial PFC stimulation is capable of either increasing or decreasing the neural activity of NA medium spiny neurons (MSNs; the main output neurons of NA). Gruber, Powell, and O’Donnell [364] performed intracellular recordings from the NA of anesthetized rats while also electrically stimulating different parts of the medial PFC along the dorsal–ventral region comprising the PL and IL areas. Electrical stimulation at some sites increased the neural spiking of a particular MSN, while stimulation of neighboring sites (the two sites were about 0.5 mm apart) resulted in inhibitory effects. The authors suggested that different neurons in the rat medial PFC can either activate MSNs directly or inhibit MSNs indirectly through excitatory projections to inhibitory interneurons (the NA contains GABAergic and cholinergic inhibitory interneurons that synapse on MSNs). These possibilities are shown in Figure 1.17(B). This study lacked the anatomical detail needed to discern the exact regions of the medial PFC involved in these disparate effects. In support of these neurophysiological findings, a recent behavioral study has shown that activation of different parts of the medial network of the rat’s PFC can either increase or decrease appetitive or aversive responses mediated by the NA-VP circuit [806].

In conclusion, different neurons in the medial PFC are capable of either increasing or decreasing the output of specific amygdala and nucleus accumbens circuits, allowing it to exert significant control over motivation and emotion. Since the medial PFC also projects to the hypothalamus, this would be another route for
a PFC influence over appetitive and avoidance responses.

1.3.5.3 The PFC and Value-Based Decision Making

Within different contexts or situations, different voluntary goal-directed responses may vary in their positive or negative consequences, and such outcomes may also change over time. That is, situation-specific responses may vary in their resultant benefits and costs, and adaptive behavior should operate over time to maximize an individual’s benefit/cost ratio. A growing body of literature indicates that the PFC is involved in such value-based decision making, and that different PFC circuits may influence different aspects of such decision making [842, 846, 1010]. The idea is that an individual’s ongoing experiences are interpreted by PFC neural mechanisms, which then exert influences on the amygdala, NA-VP, or other regions to modify the way we act.

In the study by Amemori and Graybiel [25], under different stimulus conditions, a particular approach response resulted in different benefits (liquid reward magnitude) and costs (strength of an air puff). The monkey had to decide whether to make an approach or an avoidance response based on the predicted outcomes. Although this study examined the role of the medial PFC in these behavioral choices, the cognitive processes were complex and involved both stimulus-outcome associations and response-outcome associations. Recent work has provided evidence that the orbital network (central and lateral parts of the orbital PFC) is most concerned with learning and representing the relationship between stimuli and outcomes, while the medial network (medial PFC) is most concerned with learning and representing the relationship between particular responses and their outcomes. In the study by Rudebeck et al. [842], rhesus monkeys engaged in one of two tasks. In the first, the performance of one response resulted in a greater likelihood of reward than the performance of a different response. In the second task, while holding the type of response constant, performing the response in the context of one stimulus resulted in a greater probability of reward than performing the response to a second stimulus. Monkeys with lesions to the medial PFC, focused on area 24, exhibited deficits in maximizing their receipt of reward under task 1 (response-reward associations), while monkeys with lesions to the central part of the orbital PFC showed deficits in maximizing reward receipt during task 2 (stimulus-reward associations).

If one were to view the amygdala as assigning either a positive or negative motivational valence to a stimulus, while the NA-VP circuit might be concerned with the valence value of a response (regulating approach versus avoidance), it is interesting to speculate that orbital network projections to the amygdala might regulate complex decision making by updating stimulus-outcome associations that change over time, while medial PFC projections to ventral striatal circuits might regulate complex decision making by updating and selecting responses that have the most favorable outcomes. In other words, the executive or regulatory functions of the PFC, through connections with the amygdala and ventral striatum, might update or modify the value of particular stimuli and responses, respectively, with regard to their associated outcomes. Although there is some evidence for such proposals, the detailed circuitry mechanisms, such as those described for medial PFC control over the CFR, have not been described.

Orbital PFC output to the amygdala might modulate whether a particular stimulus activates positively or negatively valent amygdala neurons, and the degree to which such neurons are activated. In the section on the functional anatomy of the amygdala, experiments by Schoenbaum et al. [869], where rats learned a go–no go response to particular odors, were reviewed. Briefly, it was found that some neurons in the BLA responded to odors signaling reward, while others responded to odors signaling aversive
consequences. More importantly, when reversal learning occurred, where a previously positive odor began to signal aversive consequences, the BLA neurons that had previously responded to the positive odor ceased to do so. Relevantly, when Saddoris, Gallagher, and Schoenbaum [848] lesioned the lateral orbital PFC on one side of the brain, the neural responses occurring in BLA during reversal training were slow to occur, suggesting that such changes were in part regulated by input from the orbital network [870].

With respect to medial PFC output to the striatum, this circuit might regulate the degree to which a particular stimulus activates the appetitive/approach or avoidance/rejection circuits that were described previously for the NA-VP regulation of behavior. It should be obvious that under natural conditions, most cases of value-based decision making are probably complex, with variations in the consequences associated with stimuli and responses occurring at the same time, so that the orbital and medial networks of the PFC would be working in concert [25]. However, careful experiments have begun to delineate the specific functional roles of each network. An important take-home message is that the PFC functions to modulate behavioral choices based on the predicted outcomes or consequences of particular acts within specific contexts.

1.3.5.4 Relevance of PFC Mechanisms to Social Behavior

Although much will be said about PFC projections to the amygdala, NA-VP circuit, and hypothalamus in subsequent chapters, it will be worthwhile to introduce the importance of such a PFC top-down regulation for social behavior at this point. If a stranger were to wink at your spouse, would it be appropriate to start a fight with that stranger? But if the stranger grabbed your spouse, what would you do? If a man passed an unfamiliar attractive woman on a deserted street, would it be appropriate for him to approach her and make sexual advances? As a very hungry visitor at a Thanksgiving dinner, if you were served first, would you take all of the white meat for yourself before passing on the serving plate to others? With respect to employment, would you call in sick often in order to engage in other activities that you deemed as immediately more rewarding, such as going to the movies? Finally, would you risk your family’s life savings on a gambling deal that could have a super-large payoff but might also result in the loss of your entire savings? All of these examples exemplify how social context can influence behavioral choices, including social behavior, which might be mediated by interactions between PFC, amygdala, ventral striatum, and hypothalamus. Interestingly, the answers to most of the questions posed involve the classic view of PFC downregulation of subcortical and allocortical circuits that regulate basic motivational and emotion states.

The classic case of Phineas Gage is an early example of the process being described. Gage was a railroad worker whose brain was damaged during a construction accident in 1825. A recent analysis of Gage’s skull has been used to reconstruct the most likely location of the brain damage, with the conclusion that the ventromedial PFC, probably involving aspects of both the medial and orbit networks, but sparing the lateral PFC, was bilaterally damaged [212]. Prior to the accident, Gage was intelligent, reliable, and socially adapted. He underwent a dramatic change in personality and social behavior after the accident. Although his language ability and intelligence remained normal, he became irresponsible and impulsive, he could not hold a steady job, and he disregarded social conventions. His physician described his symptoms as a break between his intellectual faculty and his animal propensities [212,319].

The effects of damage to the ventromedial PFC on human social behavior and decision making have been examined more recently by Damasio and colleagues [29,76,77,860]. The areas of the PFC that were damaged in these patients...
included medial, central, and lateral orbital regions, and areas 25 and 32 of the medial PFC. In a gambling task, patients with such lesions were compared to normal controls [77]. Using play money, subjects were instructed to select cards from one of two decks in order to maximize their profits. When cards were selected from one deck, the immediate reward was large, but periodically this reward would be accompanied by a large monetary penalty. The reverse was true for selecting cards from the other deck, where individual rewards were modest, but the periodic penalties were small. Over the long run, selections from the second deck would result in a monetary gain, while selections from the first deck would result in a monetary loss. Normal controls, over a long series of card selections, chose more cards from the second deck, while ventromedial PFC damage was associated with choosing more cards from the first deck. The authors suggested that PFC damage results in poor decision making because the patient’s behavior is guided to a greater extent by the immediate consequences rather than by the long-term consequences of one’s actions. Bechara et al. [76] similarly suggest that such patients fail to have anticipatory emotional experiences to the consequences of poor choices. Perhaps these patients cannot imagine the aversive nature of a strong punishment. It should be obvious how such a behavioral profile could have negative consequences for social decision making. It is intriguing to speculate that damage centered on area 32, which may be the homolog of the rodent prelimbic area, decreased anticipatory fear, as would be proposed based on the work of Milad and Quirk [645], who reported that prelimbic activation enhances the CFR in rats.

In relation to this interesting idea, in fMRI studies, Eisenberger [268] describes an increased BOLD response in the dorsal ACC, centered in areas 24 and 32, in response to social exclusion. She suggests that these regions are part of a neural network that mediates emotional pain or feelings of social distress associated with social rejection or with the dissolution of social bonds in humans. Since the rodent research shows that increased activation of the PL cortex (area 32 in humans) is associated with increases in fear-related processes, this proposal makes sense.

Interestingly, early onset damage to the PFC produces much more severe deficits in value-based decision making and social behavior than does adult onset damage. Individuals with adult damage usually do not harm others, and they have intact knowledge about appropriate social behavior (that they learned prior to the brain damage), but they make faulty decisions in the social and nonsocial realms because they appear to be guided by the immediate consequences of their actions. In contrast, individuals that received damage to the ventromedial PFC early in life do not have intact knowledge of appropriate social behavior, and they display an increased tendency toward stealing and exhibiting aggressive outbursts, risky sexual behavior, and poor parental behavior [29]. These results suggest that while the output of the ventromedial PFC to the amygdala and NA may regulate value-based social and nonsocial decision making, its outputs to other brain regions (the lateral PFC, for example) may be involved in the development of social knowledge and moral reasoning (perhaps as a result of the feedback the ventromedial PFC receives from the amygdala, which may be signaling the positive and negative consequences of one’s actions: see Figure 1.15). When both of these functions are disrupted as a result of early brain damage, social behavior would be more severely affected.

Earlier in this chapter I reviewed the data showing that patients with Williams syndrome are hypersocial and have increased amygdala reactivity to positive facial expressions and decreased amygdala reactivity to negative facial expressions. A recent fMRI study suggests that these alterations in amygdala processing of social stimuli may in part be the
result of a dysfunction of PFC control of the amygdala [672].

Finally, an interesting study on male rhesus monkeys provides evidence that medial PFC lesions decrease a monkey’s responsiveness to social stimuli [843]. Normal male monkeys retrieve a desired food item with a short latency, but if they are concurrently shown a film of a sexually active female or another male, their food retrieval latencies increase, presumably because of their interest in the social stimuli. Such an increased latency was not observed in monkeys with lesions centered on areas 24 and 32 of the anterior cingulate cortex. Therefore, parts of the primate medial PFC seem to be important in regulating social responsiveness, perhaps through interactions with amygdala, NA-VP, and hypothalamic motivational and emotional networks.

To sum up, the PFC is obviously a complex neural region, and in humans, areas 24, 25, and 32 seem to be involved in functions that include the regulation of fear-related processes and social behavior. It is possible that the regulation of emotional processes is primary, which, in turn, affects social behavior. However, the medial and orbital PFC are composed of functionally heterogeneous populations of neurons that are likely to be involved in many other processes that also impact sociality.

1.4 CONCLUSIONS

This primer of functional neuroanatomy was meant to provide a comprehensive introduction to some of the most important neural functions that will be shown to influence social behavior. I have emphasized the roles of both the amygdala and the mesolimbic DA system in both goal-directed approach and avoidance responses and described the various nuclei of the hypothalamus as providing a significant activating force on VTA-DA neurons that project to NA. The modulatory role of different parts of the PFC is capable of either upregulating or downregulating activity in the amygdala, NA-VP circuit, and hypothalamus. I have also emphasized the importance of understanding the microcircuitry within neural regions, and how neural influences on this microcircuitry regulate the output of one neural region to another. Finally, the neural regulation of basic motivational and emotional processes in nonsocial settings may overlap with the regulation of social motivational and emotional processes.