wrist movement. It is known that such a transformation takes place in a neural circuit that is formed by the inferior parietal lobule and the inferior premotor area. It is, however, not known how the transformation takes place.

FUNCTIONAL CONSEQUENCES OF DAMAGE TO THE MOTOR CORTEX

Despite the skull's bony protection of the brain, each year in the United States about 200,000 people sustain severe head injuries and another 400,000 suffer strokes.

![Damage to the motor cortex disrupts voluntary movements.](image)

Whether the damage is the result of head injury, stroke, brain tumor, brain cancer, or neurosurgical interventions, a pure pyramidal lesion is rare. Thus, many of the motor disturbances following head injuries, stroke, or other causes are the result of the involvement of both extrapyramidal and corticospinal systems. However, if the corticospinal tracts are selectively lesioned in an experimental animal, the result is loss of muscle tone (flaccid paralysis) and absence of reflexes in the involved parts. Because finger dexterity depends critically on the motor cortex, it is among the motor skills most disturbed by pyramidalotomy or any injury to the motor cortex. This motor deficit is profound and permanent. Patients with such a lesion can never again move their fingers individually to tie shoelaces, button buttons, or manually use or manipulate utensils. Voluntary movements require a functioning motor cortex.
THE NIGROSTRIATAL AND MESOLIMBIC TRACTS

Anatomy

Two major dopaminergic tracts, ascending in parallel from the midbrain to the heart of the forebrain, are very important for self-initiation of movements and for motivation, respectively.

Cell bodies of the nigrostriatal tract lie in the substantia nigra pars compacta (SNc) of the midbrain, designated A9. These neurons contain neuromelanin, which gives them a black appearance and, therefore, their name. Their axons ascend to the caudate nucleus and putamen (collectively termed the dorsal striatum), which are part of the basal ganglia (Figure 10-1).

Cell bodies of the mesolimbic tract (also referred to as the mesocorticolimbic tract) lie adjacent to the substantia nigra in the ventral tegmental area (VTA, A10); their axons ascend to the nucleus accumbens (ventral striatum), the olfactory tubercle, several limbic structures, and the prefrontal cortex (Figure 10-2).

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THE NIGROSTRIATAL/BASAL GANGLIA SYSTEM

The nigrostriatal/basal ganglia system contributes to the triggering of self-initiated movements and to postural adjustments.

It consists of both direct and indirect pathways.

Direct Pathway

The direct pathway is a positive feedback loop, by which cortical areas that initiated the activity are further excited.

There are two consecutive inhibitory influences, followed by an excitatory influence (Figure 10-3).
Sensorimotor cortex

**Putamen**

\[ D_1 \]

\[ \text{SNc} \]

\[ \text{VL/VA} \]

**GPI/SNr**

**Direct Pathway**

\[ = \text{inhibitory} \]

\[ \text{inhibitory} \]

When putamen inhibits GPI/SNr, VL/VA is disinhibited. Thus, VL/VA excite sensorimotor cortex.

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**Figure 10-3**

Nigrostriatal direct pathway.

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Stimulating the first inhibitory path (striatum to globus pallidus internal segment, GPi) inhibits the second inhibitory path (GPI to ventrolateral and ventral anterior nuclei of the thalamus, VL/VA), thereby disinhibiting the final excitatory path (thalamus to somatosensory and motor cortex). Therefore, the cortical areas that initiate a movement are able to augment that process via the direct pathway.

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**Indirect Pathway**

The *indirect pathway* is a negative feedback loop.

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It may seem counterintuitive to have opposing direct and indirect pathways. However, they may either sharpen the influence on behavior, much like the sharpening of receptive fields in the visual system, or they may provide greater control over movement, similar to having both inhibitory and excitatory postsynaptic potentials (IPSPs and EPSPs) on the same neuron.

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**The Role of Dopamine**

*Dopamine* has an excitatory effect on the direct (excitatory) pathway via \( D_1 \)-like receptors and an inhibitory effect on the indirect (inhibitory) pathway via \( D_2 \)-like receptors. Thus, both effects increase the output of the system.

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In the case of the nigrostriatal/basal ganglia system, dopamine enhances the initiation of movements, and in the case of the mesolimbic system, it increases motivation and/or reward (Figure 10-5).
**Input to the Nigrostriatal and Mesolimbic Tracts**

Major excitatory influences are from the prefrontal cortex to the nucleus accumbens and from the sensorimotor cortex to the dorsal striatum, with glutamate as the transmitter, and from the pedunculopontine nuclei in the pons, with acetylcholine as the transmitter.

Therefore, either the prefrontal or sensorimotor cortex or the pontine reticular formation can activate the direct and indirect pathways. The primary excitatory input to the dopamine cells is from the reticular formation, which responds to any sudden or important stimulus.

Major inhibitory inputs are from GABAergic neurons in the dorsal and ventral striatum and from the dopamine cells themselves, which release dopamine from their dendrites, cell bodies, and axon terminals, all of which contain inhibitory autoreceptors.

Both of these sources of inhibition are therefore negative feedback loops.

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**Postsynaptic Actions of Dopamine**

Dopamine does not directly excite or inhibit postsynaptic neurons. Rather, it alters the voltage sensitivity of voltage-sensitive K⁺ channels.

D₂ receptors shift the threshold to a lower membrane voltage, so that the outward flow of K⁺ is less likely to occur, and the neuron is more responsive to depolarizing input. With depolarization, the Mg²⁺ block of N-methyl-D-aspartate (NMDA) receptors is removed, and they are therefore more likely to be activated by glutamate. Thus, stimulation of D₂ receptors enables the excitatory influence from the cortex to activate the direct pathway. On the other hand, stimulation of D₁ receptors has the opposite influence, rendering the postsynaptic neurons less excitable. Because D₂ receptors are located primarily on neurons forming the initial segment of the indirect (inhibitory) pathway, dopamine will inhibit that pathway, with a resulting disinhibition of the thalamocortical path.

Therefore, dopamine (via D₁ receptors) activates the direct pathway and (via D₂ receptors) inhibits the indirect pathway.

Both of these actions result in enhanced ability to initiate movements or increased motivation.

Dopamine in the dorsal and ventral striatum arises from both synaptic and nonsynaptic (axon varicosities) sources. Dopamine diffuses some distance from the site of release, resulting in volume conduction of the neurotransmitter. There are two firing modes of nigrostriatal and mesolimbic neurons: phasic and burst firing. Phasic release is directly related to the firing rate of the dopamine neurons. Burst firing increases dopamine release exponentially. However, heteroreceptors on dopamine terminals modulate dopamine release, either increasing or decreasing the amount of neurotransmitter released in response to action potentials. There is a strong correlation between firing rate and motor activity, and the increases in firing rate frequently anticipate motor activity.

**Detection of Dopamine: Methods**

Because dopamine diffuses from its site of release, dopamine overflow can be detected by either microdialysis or voltammetry.
In microdialysis, artificial cerebrospinal fluid is pumped very slowly into a probe, which has a closed "sock" of dialysis membrane attached to the end. Because the end of the membrane is plugged, the fluid must return up a (usually concentric) length of very fine silica tubing, which in turn ends either in a collecting tube or an on-line injector. During the time the fluid is in the dialysis membrane sock, small molecules, such as monoamines and their metabolites, can diffuse from the extracellular fluid into the dialysate. Conversely, drugs can be delivered into the brain from the dialysate. Neurotransmitters and their metabolites can be detected in the dialysate using electrochemical detection. Microdialysis provides an accurate estimate of several neurotransmitters and their metabolites. However, the sampling time is relatively long (usually 3 to 20 min), and the membrane socks are relatively large (210 μm in diameter and 1 to 3 mm in length) (Figure 10-6).

Voltammetry employs carbon fiber electrodes coated with a substance that selectively allows oxidation of dopamine. It has a much shorter sampling time (fractions of seconds) than microdialysis and much finer spatial resolution. However, it does not have complete specificity regarding the molecule being measured and cannot provide assessments of multiple transmitters.

The third major technique for studying dopaminergic influence is single neuron recording of dopamine cell bodies. This technique provides excellent time resolution and a quantitative measure of neuronal activity. However, it does not reflect the spatial distribution of the terminals or the influence of heteroreceptors on release.

![Microdialysis probe](Image)

**Figure 10-6** Microdialysis probe.

### Parkinson Disease

Degeneration of the nigrostriatal tract results in Parkinson disease, which is characterized by tremor at rest, difficulty initiating movements, rigidity, postural instability, and cognitive problems.

Patients frequently lose 80% of the nigrostriatal neurons before symptoms appear. The reason for the late appearance of symptoms is that the dopamine systems are able to compensate for the loss of neurons by increasing synthesis and release of dopamine in the remaining neurons and by increasing postsynaptic receptors. Some cases of Parkinson disease are based on inheritance. However, the most apparent to be related to environmental toxins, drugs, and trauma, or to unknown factors. Dopamine, itself, can be metabolized to produce free radicals and H₂O₂, which lead to membrane disruption. Therefore, the increased dopamine synthesis and metabolism in the remaining neurons may actually be toxic for the neurons, leading to a downward spiral of symptoms.

The standard treatment for Parkinson disease is administration of L-dopa, the precursor of dopamine. However, although this alleviates symptoms, it also increases metabolism of dopamine, thereby contributing to the potential toxicity. The dopamine agonist apomorphine has been used with some success. There have been two types of surgical treatments for Parkinson disease. First, tissue from either human fetuses or the patient's own adrenal medulla has been grafted into the caudate nucleus. The patients who benefited most from this procedure were relatively young, with a recent (in several cases, drug-induced) onset of the disease. The other surgical treatment is to make a lesion in the STN or the GPe/substantia nigra pars reticulata (SNr). Because STN excites GPe/SNr, which in turn inhibits the VL/VTA nuclei of the thalamus, a lesion of either STN or GPe/SNr would disinhibit the thalamocortical excitation. Strangely enough, stimulation of these structures, via surgically implanted electrodes, has effects similar to those of lesions. However, one possibility is that the stimulation may, in fact, produce a functional lesion.

### The Mesolimbic System

The mesolimbic dopamine tract parallels the nigrostriatal dopamine tract.

It begins in the VTA of the midbrain, adjacent to the substantia nigra, and ends in the nucleus accumbens (NAcc), or ventral striatum. It also has terminals
in the olfactory tubercle, in several limbic system structures (amygdala, lateral septum, and bed nucleus of the stria terminalis), as well as in the prefrontal cortex. This chapter will focus primarily on the terminals in the NAcc, because most of the research on the mesolimbic tract has been similarly focused.

Whereas the nigrostriatal tract primarily facilitates self-initiated movements, the mesolimbic tract increases responsiveness to internal and external stimuli and promotes motivation for numerous goals.

It may also contribute to the sense of reward after achieving those goals. This tract also plays a role in drug addiction and schizophrenia.

**Direct Pathway**

The direct pathway in the mesolimbic system begins in the NAcc, which in turn inhibits the ventral pallidum.

This results in disinhibition of the mediiodorsal (MD) thalamus of the thalamus, which excites the prefrontal cortex (PFC). Thus, in both the nigrostriatal and mesolimbic systems, stimulation of the direct pathway results in excitation of the sensorimotor or prefrontal cortex. Although the relative distributions of the D1 and D2 families of receptors in the direct and indirect pathways have been investigated less thoroughly in the mesolimbic system than in the nigrostriatal system, similar patterns of distribution in the two systems have been reported. Furthermore, the known properties of the D1 receptor suggest that it may play a similar role in the two systems (Figure 10-7).

**Indirect Pathway**

The indirect pathway is, again, a negative feedback loop.

It, too, begins with two inhibitory paths [NAcc to ventral pallidum (VP), and VP to STN]. This disinhibits an excitatory path (STN back to VP). Thus, activation of the first inhibitory pathway results in disinhibition of an excitatory path-

way. However, this excitatory pathway ends on another inhibitory path [VP to mediiodorsal (MD) thalamus]. Because the thalamus normally excites the cortex, inhibition of the thalamus results in less input to the cortex, thereby inhibiting motivation. The dopamine receptors on the first inhibitory tract of the indirect pathway are probably of the D2 subtype. Because these receptors shift the threshold for the voltage-gated K+ channels to a less polarized level, the outward flow of K+ will counter depolarizing influences, and therefore tend to inhibit the post-synaptic cells. Thus, stimulation of D2 receptors in the NAcc will inhibit the indirect pathway, thereby removing a negative feedback loop. Because stimulation of D1 receptors facilitates the excitatory direct pathway, and stimulation of D2 receptors tends to inhibit the inhibitory indirect pathway, both actions of dopamine will enhance the excitatory input from the mediiodorsal thalamus to the prefrontal cortex (Figures 10-8 and 10-9).

The nucleus accumbens is divided into a core and a ventromedial "shell" region. The core appears to be more concerned with the motoric expression of motivation, whereas the shell is considered to be part of the extended amygdala (a major limbic system structure) and is important for the acquisition of incentive learning and for primary reward (Figure 10-10).
The Nigrostriatal and Mesolimbic Dopamine Tracts

Figure 10–10
Coronal view of the rat brain at the level of the NAcc. Cpu, caudate putamen.

The Role of Dopamine in Goal-Directed Behaviors

Dopamine is thought to increase responsiveness to both external and internal stimuli.

It may also contribute to reward. If dopamine is the major transmitter mediating reward processes, the firing rate of dopaminergic neurons should increase after food or drug delivery and decrease before the next response. This is, indeed, the pattern observed during the first several reinforcements (Figure 10-11A). Similarly, dopamine levels are elevated within a couple of minutes after application of tail pinch, showing that dopamine is also released in response to aversive stimuli and stress (Figure 10–11B). However, after an animal learns to bar press for a reward, dopamine neurons begin to increase their firing rate before the bar press and actually decrease firing when the reward is delivered (Figure 10–12). These data suggest that dopamine is more important for the behavioral activation that secures the goal (or avoidance of aversive stimuli) than for mediation of the reward itself. Consistent with this hypothesis, it has been reported that both nigrostriatal and mesolimbic neurons fire in response to novel attention-grabbing stimuli within almost any stimulus modality. This dopaminergic activity would arouse the motivational fervor of an animal to respond to whatever stimulus is appropriate at the moment. It may also signal the unpredictability of a stimulus and may lead to permanent changes in the dorsal and ventral striatum.

On the other hand,

dopamine may also mediate important aspects of reward.
Figure 10-11
Dopamine levels in the nucleus accumbens of rats, measured with in vivo voltammetry. 
(A) Dopamine levels before and after presentation of food. (B) Dopamine levels before, 
during (between vertical lines), and after tail pinch. In both cases, dopamine levels 
begin to rise within 2 min of presentation of the stimulus. (From E.A. Kiyatkin, Neurosci 
Biobehav Rev 1995; 19:573.)

Figure 10-12
Dopamine levels in the nucleus accumbens of rats that have been trained to bar press 
for cocaine or food. Dopamine levels rise until the bar press, after which they decline. 
Vertical lines represent the time of the bar press; dashed lines indicate dopamine 
levels at the time of the previous bar press. (From E.A. Kiyatkin, Neurosci Biobehav 
Rev 1995; 19:573.)
All classes of abused drugs increase extracellular dopamine in the NAcc via diverse mechanisms. They also decrease the threshold for electrical brain stimulation reward (i.e., making it easier for the rewarding effect to occur). Conversely, dopamine antagonists, microinjected into the NAcc, decrease brain stimulation reward. Finally, microdialysis shows an increase in dopamine in the NAcc during exposure of a male rat to an estrous female and a further increase during copulation. Thus, dopamine is released during both the appetitive and consummatory (or rewarding) aspects of behavior. Therefore, dopamine may play a role in both the motor activation required to achieve a goal and in the reward itself.

We have seen that dopamine neurons fire before and/or after numerous types of motivation behavior. Is the system able to discriminate among the types of behavior and/or the types of reward? Neurons in the NAcc and prefrontal cortex have been recorded during sessions in which rats self-administered either cocaine or heroin. Very different patterns and timing of activity have been observed, both within and across neurons, as motivational state and incentive or rewarding stimuli were changed. In some cases neurons fired during presentation of stimuli predictive of reward, and in other cases they fired during presentation of the reward itself. Because the firing of dopaminergic neurons appears to be similar across different motivational states, the discriminative nature of NAcc responses suggests that some specificity is conferred by input from the cortex to the NAcc. Thus, dopamine appears to be generally enabling of responses to gain a reward and of the reward itself. On the other hand, the postsynaptic neurons in the NAcc are able to discriminate among rewards and among different phases of conditioning. Similarly, dopamine in the nigrostriatal tract does not carry specific information about motor patterns, but rather enables the cortex to plan and initiate those patterns.

The Role of the Mesolimbic Dopamine System in Drug Addiction

Mesolimbic dopamine is also important in drug addiction.

Acute administration of cocaine, amphetamine, morphine, ethyl alcohol, and nicotine all increase extracellular dopamine in the NAcc. These drugs also facilitate intracranial electrical self-stimulation (rewarding electrical stimulation of the brain) via dopaminergic mechanisms. Finally, withdrawal from various abused drugs results in decreased extracellular concentrations of dopamine in the NAcc and increased reward threshold.

Numerous cellular changes result from chronic drug administration. These include increased tyrosine hydroxylase (TH, the rate-limiting enzyme in dopamine synthesis) in the VTA (resulting in more dopamine to stimulate autoreceptors on dendrites and cell bodies and therefore decreased firing rate and decreased dopamine release at the terminals in NAcc) and decreased TH in the terminals in the NAcc. The decrease in TH in the NAcc may result from decreased neurofilaments in dopaminergic axons and therefore decreased axonal transport (Figure 10–13).

Together, these findings suggest that the release of dopamine in the NAcc may produce the rewarding effects of abused drugs and that the decrease in dopamine during drug withdrawal produces the dysphoria characteristic of that state. However, things are not as simple as that.

First, self-administration of opiates is not blocked by dopamine antagonists, suggesting that nondopaminergic synapses mediate opiate reward. However, conditioned place preference for opiates is blocked by dopamine antagonists. In conditioned place preference, an animal is injected with either a drug or saline as
a control. It is then placed into one of two distinctive boxes; drug injections are always followed by placement into one box and saline injections are always followed by placement into the other. After a number of such pairings, the animal is tested in a drug-free state. It is placed into an alley that connects the two boxes and chooses which box to spend more time in. Drugs of abuse, including opiates, reliably result in a greater choice of the box previously associated with drug injections, and this is blocked by dopamine antagonists administered before each drug injection. Therefore, dopamine may be important for the learning of drug-stimulus (the correct box) associations for most abused drugs, although it may mediate the self-administration only of psychostimulants (amphetamine and cocaine), which are indirect dopamine agonists.

A second problem with the dopamine hypothesis of drug withdrawal is that the state of decreased dopamine release during withdrawal should impair all types of motivation, including that for more drug. It is true that motivation for conventional reinforcers is diminished during withdrawal and that the threshold for rewarding electrical brain stimulation is raised (requiring more intense stimulation to elicit reward). However, there is actually an intense craving for drugs. It has been proposed that the difference between conventional reinforcers and abused drugs is that dopaminergic and behavioral responsiveness to conventional reinforcers becomes satiated, whereas drugs short-circuit the neural chain that produces the satiation. This may reinforce the learning of drug-stimulus associations, at the expense of conventional reinforcers.

It has been suggested that the drug craving may be increased by activation of D_2 receptors in the NAc and decreased by activation of D_1 receptors there.

In an experiment rats were trained to press a lever to deliver intravenous cocaine in a daily 4-hour schedule. For the first 2 hours cocaine was freely available; during the second 2 hours, saline was substituted. During the saline phase, responding decreased (extinction) (Figure 10–14).

After the decrease in responding, animals were given injections of either a D_1- or a D_2-like agonist to determine whether these drugs would reinstate responding for the saline intravenous infusions. The D_2-like agonist did result in large increases in responding. Therefore, stimulation of D_2-like receptors triggered a relapse (induced craving). The D_1-like agonist did not increase responding at all. Therefore, D_1-like receptors are not implicated in producing craving. Next, the D_1- or D_2-like agonists were given during the saline phase 30 min before an intravenous injection of cocaine to determine whether these agonists would increase or decrease the response to cocaine (Figure 10–15).

The D_2-like agonist greatly increased the responses following the cocaine priming dose. However, the D_1-like agonist completely blocked responding following the cocaine primer. Therefore, the D_2-like agonist not only did not elicit responses, it actually decreased the effectiveness of cocaine.

In other experiments, both D_1- and D_2-like agonists were self-administered by rats and therefore produced rewarding effects of their own. Therefore, the inhibitory effects of the D_1-like agonists on cocaine self-administration were not accompanied by an inhibition of reward. This is especially interesting, because such agonists could be used to treat cocaine addiction. Dopamine agonists have previously been proposed as possible treatments for cocaine abuse, because they can block the rewarding effects of psychostimulants; however, these agonists exacerbate withdrawal symptoms and are aversive to both rats and humans. Therefore a better treatment for drug abuse may be D_1-like agonists, which produce rewarding effects of their own but decrease the craving for cocaine.

![Diagram](https://example.com/diagram.png)

**Figure 10–14**
Effects of intraperitoneal priming injection with vehicle (saline), the D_2-like dopamine agonist 7-hydroxy-di-n-propylnorphetamine (7-OH-DPAT, 3 mg/kg), or the D_1-like agonist SKF 92958 (1 mg/kg) on reinstatement of nonreinforced lever-press responding in a representative animal. Priming injections were given after extinction from 2 hours of intravenous cocaine self-administration, when only intravenous injections were available. Hatchmarks denote the times of each self-infusion of cocaine in the cocaine phase and of saline in the saline phase. (From D.W. Self et al., Science 1996;271:1586.)
The Role of the Mesolimbic Dopamine System in Schizophrenia

Symptoms of schizophrenia are divided into two groups: positive symptoms and negative symptoms.

Positive symptoms (characteristics that are abnormal in their presence) include hallucinations, delusions, and thought disorder (consecutive thoughts that have little relationship to one another). Negative symptoms (characteristics that are abnormal in their absence) include flat affect and social withdrawal.

Numerous brain abnormalities are characteristic of schizophrenia.

Brain volume is decreased, particularly in cortical gray matter, amygdala, hippocampus, and thalamus. Conversely, the lateral and third ventricles are increased in volume (signifying decreased brain tissue). In addition, an abnormal orientation of neurons has been observed in the hippocampus and the surrounding entorhinal cortex. Finally, inappropriate expression of various peptides has been reported.

In spite of the multiple brain abnormalities in schizophrenia, a single hypothesis has dominated much of the thinking about its cause.

The dopamine hypothesis of schizophrenia proposes that increased levels of, or receptors for, dopamine in the dorsal and/or ventral striatum underlie the disorder.

The primary evidence for this hypothesis is that dopamine antagonists are used to treat psychotic symptoms, whereas dopamine agonists induce or exacerbate such symptoms.

However, there are several problems with the dopamine hypothesis. First, there are different time courses of the effects of antipsychotics on symptoms of schizophrenia compared with those on dopamine synapses. It takes approximately 2 weeks for these drugs to improve symptoms of schizophrenia; however, the drugs block dopamine receptors almost immediately. Second, most typical antipsychotics are more effective in treating positive than negative symptoms. However, some atypical antipsychotics are reported to relieve negative as well as positive symptoms. Third, there is no evidence for increased dopamine levels in the brains of schizophrenics, although there may be increased D₃ receptors in the NAce. Fourth, there are widespread anatomical abnormalities, including disarrayed neurons in the hippocampus, larger ventricles, and lighter brain weights. It is not clear how alterations of dopamine could affect brain anatomy.

A recent, more integrative hypothesis proposes that the anatomical abnormalities in schizophrenics reflect deficiencies in neural processing that provide input to the ventral striatum.
Specifically, hallucinations and delusions may result from excessive activity in the hippocampus and surrounding temporal neocortex. These may be assigned undue emotional relevance, due to overactivity in the extended amygdala. Because the prefrontal cortex is hypoactive, it is unable to evaluate and inhibit these excesses. As a result, the ventral striatum is bombarded with incoherent sensory and motivational inputs. In support of this theory, medications that ameliorate the positive symptoms of schizophrenia result in modulation of DNA transcription in the shell of the NAcc, where inputs from the amygdala and the prefrontal and temporal cortices converge. Furthermore, postmortem, neuropsychological, and neuroimaging studies have revealed hyperactivity of the temporal cortex, associated with reality distortion, and hypoactivity of the prefrontal cortex, associated with negative symptoms and poor impulse control.

SUMMARY

In both the nigrostriatal and mesolimbic dopamine systems, dopaminergic activity increases activity in thalamocortical positive feedback pathways. Dopaminergic activity in the nigrostriatal system enhances the ability of the sensorimotor cortex to initiate movements. Degeneration of this tract in Parkinson disease results in impairment of self-initiated movements, among other symptoms. Dopamine in the mesolimbic system promotes behavioral responsiveness to many motivational stimuli and may also mediate or enhance the rewarding characteristics of those stimuli. Dopamine is released following unexpected rewarding stimuli, such as food and psychoactive drugs, or aversive stimuli, or leading up to responses to obtain rewarding stimuli. Drugs of abuse typically increase extracellular levels of dopamine in the mesolimbic system, either directly or indirectly. Furthermore, drug addiction is characterized by decreased dopamine release from mesolimbic neurons, which may promote a state of dysphoria. Finally, excess stimulation of D2 dopamine receptors in the mesolimbic system, coupled with hypoactivity of the frontal cortex, may contribute to schizophrenia, specifically to a hyperresponsiveness to thoughts or stimuli that give rise to hallucinations or thought disorder.