3

Glutamatergic Pathways

Their Relevance for Psychiatric Diseases

Yoland Smith

1. INTRODUCTION

Glutamate is the main excitatory neurotransmitter in the mammalian central nervous system (CNS). Its effects are mediated through a large variety of ionotropic and metabotropic receptors abundantly expressed along the whole extent of the neuraxis. Abnormal regulation of glutamatergic transmission is, therefore, a key factor that underlies the appearance and progression of many neurodegenerative and psychiatric diseases. Unfortunately, the success of therapeutic strategies aimed at modulating glutamatergic transmission has been variable owing to the widespread distribution of glutamate receptors throughout the brain and the importance of glutamate in normal brain functioning. Although the importance of glutamatergic transmission in the modulation of neuronal activity involved in processing limbic and cognitive information has long been established, the complexity of the neuronal pathways involved combined with the multifarious effects glutamate could mediate via pre- and postsynaptic interactions with various receptor subtypes, have led to important controversies regarding the exact role glutamate plays in psychiatric diseases. However, substantial progress has been made over the past 10 yr in dissecting out the anatomy, physiology, and pharmacology of various neuronal pathways whereby glutamate could functionally modulate integrative processing of complex cognitive information. This chapter briefly summarizes some of these observations and considers their implications in our understanding of the anatomo-patho-physiology of psychiatric diseases, particularly schizophrenia, for which various hypotheses based on abnormal glutamatergic/dopaminergic transmission have been put forward to explain the neurochemical dysfunction of this disease *(1–15)*.

This review does not intend to cover the whole literature on the potential implications of glutamatergic pathways in psychiatric diseases, but will rather focus on recent developments regarding the anatomy and the potential mechanisms whereby glutamatergic pathways may interact to modulate neuronal integration in cortical and subcortical brain regions known to be affected in psychiatric diseases (Fig. 1).

From: *Dopamine and Glutamate in Psychiatric Disorders*
Edited by: W. J. Schmidt and M. E. A. Reith © Humana Press Inc., Totowa, NJ

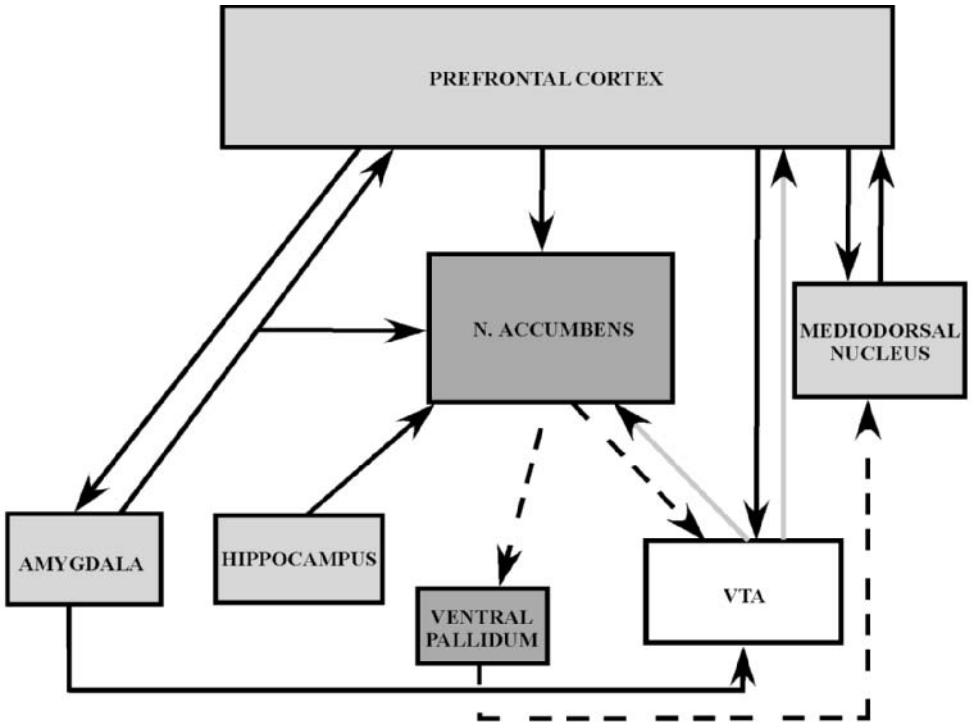

Fig. 1. Summary diagram and the main subcortical glutamatergic circuitry (black arrows) involved in the processing of limbic and cognitive information related to psychiatric diseases. These pathways play important roles in regulating dopaminergic outflow from the ventral tegmental area (light gray arrows) and γ-aminobutyric acid output from the nucleus accumbens (dashed arrows). Note that many connections have been purposefully omitted from this diagram.

2. DOPAMINERGIC/GLUTAMATERGIC HYPOTHESES OF PSYCHIATRIC DISORDERS

It has long been thought that schizophrenia and other psychiatric disorders were mediated by direct alterations of dopamine neuronal activity. This long-term belief was based on two main observations:

1. Drugs that increase dopamine levels in the brain create conditions that resemble those of schizophrenic psychosis in normals and exacerbate the psychosis problems in schizophrenic patients.
2. Drugs currently used to treat schizophrenics block dopamine receptors.

Although abnormal dopaminergic transmission remains a key component of the changes in neural activity that underlie psychiatric disorders *(14)*, it appears that the main abnormality of dopamine transmission in schizophrenics is largely mediated by changes in extrinsic regulatory influences of dopamine release either at the level of the ventral tegmental area or in the prefrontal cortex and nucleus accumbens *(1,3,5,12,14)*.

There are now various sets of data suggesting that forebrain dopamine systems may not be the primary site of neuropathology that is schizophrenia. Numerous studies have found structural and metabolic abnormalities in anterior temporal lobe and prefrontal

cortices *(8,14,16)*. Therefore, it seems that dopamine transmission is not affected in schizophrenia owing to a major defect in midbrain dopamine cell functions but rather results from an abnormal modulation by glutamatergic influences from limbic and prefrontal cortical regions (*1,3,5,12* and Chapter 7). In addition to the cerebral cortex, other forebrain structures and pathways that use glutamate as a neurotransmitter have been considered potential targets of schizophrenia and other psychiatric diseases. These include the amygdala, hippocampal formation, and mediodorsal thalamic nucleus *(6,14)*. Furthermore, the functional interactions between cortical and subcortical glutamatergic pathways at the level of the nucleus accumbens have received considerable attention over the past decades in regard to their potential involvement in neuropsychiatric diseases *(5)*. In this chapter, I will give an overview of the main features that characterize the anatomical and functional organization of these glutamatergic pathways (Fig. 1) and discuss recent findings that suggest their involvement in cognitive, emotional, and limbic-related behaviors.

3. CHANGES IN THALAMOCORTICAL AND INTRINSIC CORTICO-CORTICAL GLUTAMATERGIC CONNECTIONS IN PSYCHIATRIC DISEASES

The prefrontal cortex plays a major role in cognitive, limbic, and memory functions. Abnormalities in information processing or neurological damage to the prefrontal cortex may lead to a myriad of symptoms ranging from changes in personality traits to working memory deficits, and psychiatric diseases *(6,14)*. The anatomical organization of the prefrontal cortex in primates is very complex and comprises a multitude of functional areas characterized by differential patterns of connectivity and electrophysiological properties *(17–19)*. The activity of the prefrontal cortex is under the control of various afferent inputs that use glutamate as neurotransmitter. One of the main sources of thalamic afferents to the prefrontal cortex is the mediodorsal nucleus (MD), although projections from high-order, intralaminar and midline thalamic nuclei have also been reported *(20,21)*. The MD comprises various subdivisions and it appears that each of these subnuclei contribute to the innervation of different prefrontal cortical regions. For instance, the ventral part of the magnocellular MD (MDmc) projects to lateral regions of the ventral and medial prefrontal cortex including Walker's areas 11 and 12, whereas the dorsal part of MDmc is mainly connected with ventromedial regions of the prefrontal cortex (areas 13 and 14). In contrast, the lateral parvicellular MD (MDpc) innervates preferentially dorsolateral and dorsomedial prefrontal areas (Walker's 46, 9, and 8B); the multiform MD (MDmf) is mainly connected with area 8A, whereas area 10 has connections with the anterior part of MD. Thalamic inputs from MD are invariably confined to layer IV and adjacent deep layer III *(22)*. Interestingly, both the number of neurons and volume of MD are reduced in the brains of schizophrenic patients *(23,24)*. In line with these observations, other studies have reported fewer putative thalamic axon terminals and fewer dendritic spines on cortical pyramidal neurons in the prefrontal cortex of schizophrenics *(25,26)*. Although the exact functional implication of decreased thalamic influences on the prefrontal cortex in schizophrenia remains to be established, it has been suggested that they may lead to abnormalities in the inhibitory γ-aminobutyric acid (GABA)ergic microcircuitry of the primate prefrontal cortex *(27,28)*. However, acute lesion of the MD does not result in any significant changes in the expression of glutamic acid decarboxylase

67 (GAD67) mRNA in the prefrontal cortex of rats suggesting that the cortical abnormalities in GABAergic transmission observed in schizophrenia may be mediated by more complex changes in cortical microcircuitry than a mere decreased activity of thalamocortical glutamatergic inputs *(29)*.

The prefrontal cortex is also endowed with extensive glutamatergic corticocortical connections that may be affected in schizophrenia *(6)*. Although some of these connections involve posterior and temporal association areas, profuse horizontal axonal projections from layers II and III of dorsolateral prefrontal areas 9 and 46 to neighboring cortical areas have been described. These local projections are organized in a cluster-like manner that forms a series of elongated stripes within the same areas of the dorsolateral prefrontal cortex. Furthermore, these connections are reciprocal, suggesting that they form distinct interconnected functional modules that could play an important role in the integration and processing of prefrontal cortical information relating to working memory, one of the most fundamental cognitive process affected in schizophrenia. Although there is no direct evidence that these connections are specifically affected in psychiatric diseases, the fact that the size of layer III neuronal perikarya is reduced, combined with the evidence for a decrease in the density of dendritic spines on layer III pyramidal neurons in the prefrontal cortex of schizophrenic patients, are strong evidence in favor of abnormalities in the intrinsic glutamatergic microcircuitry in schizophrenia *(6)*.

4. GLUTAMATERGIC INPUTS TO MIDBRAIN DOPAMINERGIC NEURONS: KEY FACTORS IN CHANGES OF DOPAMINERGIC TRANSMISSION IN PSYCHIATRIC DISORDERS

Extrinsic glutamatergic inputs play a critical role in controlling the firing rate and firing pattern of midbrain dopaminergic neurons in the ventral tegmental area (VTA) *(3)*. Local application of glutamate or stimulation of glutamatergic afferents from the prefrontal cortex or the subthalamic nucleus results in an increased burst firing in midbrain dopaminergic neurons, thereby increased phasic dopamine release in the nucleus accumbens *(3,30,31)*. Midbrain dopaminergic neurons, in particular those in the VTA, receive massive glutamatergic inputs in primates *(32)*. Almost 70% of the total synaptic innervation of VTA dopaminergic neurons arises from glutamatergic boutons in monkeys *(32)*. The prefrontal cortex, subthalamic nucleus, and the brainstem pedunculopontine tegmental nucleus are likely to be the main sources of this innervation *(3,33–35)*.

The VTA is made up of largely segregated populations of dopaminergic and non-dopaminergic projection neurons that project to various cortical and subcortical brain structures, including the nucleus accumbens and the prefrontal cortex. Interestingly, glutamatergic inputs from the prefrontal cortex display a high degree of synaptic specificity in the rat VTA, targeting selectively GABA-containing mesoaccumbens neurons and dopamine-containing mesocortical cells *(36)*. These anatomical data provide a basic substrate for highly specific mechanisms through which prefrontal inputs may control the activity of ascending dopaminergic and GABAergic outflow from the VTA. It is noteworthy that the prefrontal cortex may also control the burst firing of midbrain dopaminergic neurons via its projections to the nucleus accumbens, which, in turn, sends GABAergic inputs to the VTA either directly or indirectly through disinhibition of the ventral pallidum *(3,37)*.

Other sources of glutamatergic projections that mediate changes in firing pattern of VTA neurons include the ventral hippocampus, entorhinal cortex, and amygdala, most likely via polysynaptic pathways that involve projections to the ventral striatum. However, it is important to note that the extended amygdala *(38)*, including the central nucleus and the bed nucleus of stria terminalis provides direct topographic inputs to midbrain dopaminergic neurons *(39,40)*. These represent additional routes through which glutamate could exert direct control on midbrain dopaminergic neuron activity.

5. THE NUCLEUS ACCUMBENS: A CRITICAL SITE FOR PREFRONTAL CORTICAL GLUTAMATERGIC MODULATION OF TONIC DOPAMINE RELEASE

Another way through which prefrontal glutamatergic outputs regulate subcortical dopaminergic transmission is via projections to the striatum (*see* Section 7). Corticostriatal glutamatergic afferents utilize multiple pathways to regulate striatal dopamine release and levels of extracellular dopamine *(3)*. In vitro and in vivo studies have proposed various pre- and postsynaptic mechanisms that involve both ionotropic and metabotroic glutamate receptors, as well as indirect multisynaptic pathways that could mediate these effects *(3)*. Grace and his colleagues have proposed that the glutamatergic modulation of intrastriatal dopamine release is mainly responsible for the maintenance of tonic dopamine levels in the striatum, whereas glutamatergic inputs to midbrain dopaminergic neurons regulate phasic dopamine release *(3)*. Although the prefrontal cortex is a key component for the control of intrastriatal dopamine levels, other glutamatergic inputs from the amygdala and hippocampus also appear to be involved through complex interactions functional interactions at the level of the nucleus accumbens (*see* Section 7).

6. STRESS-INDUCED DISRUPTION OF GLUTAMATERGIC TRANSMISSION FROM THE PREFRONTAL CORTEX AND ITS IMPACT FOR PSYCHIATRIC DISORDERS

Because of its functional importance in regulating dopaminergic transmission at cortical and subcortical levels, abnormal activity of prefrontal glutamatergic influences on the nucleus accumbens and the VTA may play a critical role in various psychiatric diseases *(12)*. The role of stress in the induction, maintenance, and relapse of psychiatric dysfunctions is well established and there is good evidence that changes in glutamatergic transmission in the prefrontal cortex and, possibly the hippocampus, may be responsible for the dopamine-mediated behavioral abnormalities seen in psychiatric diseases *(12)*. Stress induces two temporally different glutamate-mediated events in the prefrontal cortex. The first is an initial acute response characterized by an increase of fast glutamatergic synaptic transmission. This first event, which underlies immediate responses to stress, is likely to be induced by increased transmission of thalamocortical sensory inputs to prefrontal and limbic cortical areas *(12)*. This acute response is followed by long-lasting increases of glutamate and monoamine releases in prefrontal, limbic, and hippocampal cortices. Long-lasting changes in gene expression and protein synthesis also characterize this second event.

The prefrontal cortex also plays an important role in regulating the hypothalamo–pituitary axis (HPA) and glucocorticoid secretion during stress. It appears that the rather slow increased glutamate release in the hippocampus following stress might be mediated through HPA-regulated mechanisms, whereas the fast changes in glutamatergic transmission that

occur in the prefrontal cortex might be independent of the HPA axis and, rather, involve increased synaptic release of glutamate from intracortical or extrinsic afferents *(12)*.

7. FUNCTIONAL INTERACTIONS BETWEEN GLUTAMATERGIC INPUTS FROM THE AMYGDALA, HIPPOCAMPUS, AND PREFRONTAL CORTEX TO THE NUCLEUS ACCUMBENS

The nucleus accumbens is thought to be a key structure in the neuronal circuitry that underlies the neurobiological bases of psychiatric disorders, most particularly schizophrenia. The convergence of glutamatergic inputs from the amygdala, the prefrontal cortex, and the hippocampus, three brain regions that are affected in schizophrenic patients, combined with the dopaminergic inputs from the VTA, set the stage for multifarious and complex functional interactions that underlie the processing and integration of cognitive and limbic-related information flowing through this brain region. The anatomy and electrophysiology of these projections have been studied in great detail, which led to various hypotheses regarding the mechanisms by which these glutamatergic and dopaminergic projections interact to mediate their functional effects on behavior *(3,5)*. This section briefly summarizes some of the main anatomical features that characterize the organization and synaptic connectivity of these pathways, and discusses recent electrophysiological observations that support an important role for amygdala and hippocampal inputs to gate information flow from the prefrontal cortex to the nucleus accumbens *(5)*.

7.1. The Corticostriatal Projection

Various areas of the prefrontal and cingulate cortices provide substantial inputs to the monkey nucleus accumbens *(43–45)*. Price and his colleagues *(46)* defined the organization of prefronto-cortical projections to the striatum according to two major prefrontal networks involved in the integration and processing of functionally different information. These two networks are characterized by different corticocortical connections and distinct connections with subcortical brain regions including the thalamus, hypothalamus, and amygdala. The *"orbital network"* is thought to be involved predominantly in the processing of sensory information relating to food and feeding, whereas the *"medial network"* is more closely related to visceromotor or emotional motor functions *(45,46)*. The two pathways are tightly connected with various cortical and subcortical limbic structures including the amygdala, entorhinal cortex, and hippocampus, through which they may play important roles in controlling mood and guiding behaviors *(46)*. The two networks are differentially connected with the dorsal and ventral striatum. The ventromedial striatum, which includes the ventral putamen, medial caudate nucleus, and nucleus accumbens, receives its main input from the medial cortical network. Projections from caudomedial areas 32, 25, and 14r innervate mainly the medial edge of the caudate nucleus, the nucleus accumbens, and the ventromedial putamen, whereas projections from cortical areas 10o, 10m, and 11m remain restricted to the medial edge of the caudate nucleus *(46)*. Projections from areas 12o, 13a, and Iai terminate in the lateral accumbens and ventral putamen. On the other hand, projections from the "orbital network" are mainly directed toward the central part of the rostral striatum, which includes the central and lateral parts of the caudate nucleus and the ventromedial putamen *(46)*.

In addition to the prefrontal cortex, the nucleus accumbens also receives cortical inputs from limbic- and associative-related areas of the temporal lobe including the

entorhinal and perirhinal cortices, as well as the rostral portion of the superior temporal gyrus *(41,47–49)*. The cingulate cortex (areas 25, 24a–c, 24 a′–c′) is another major source of topographic cortical inputs to the monkey ventral striatum. The medial ventral striatum is mainly innervated by parts of the anterior cingulate cortex (areas 25, 24a,b) whereas the shell region of the accumbens receives fibers from areas 25, 24a,b and 24 a′,b′. Projections to the core of the accumbens arise primarily from areas 25, 24a,b and the medial part of area 24c, whereas the lateral part of the ventral striatum is mainly targeted by fibers coming from areas 24b,b′ and 23b and medial 24c *(43)*.

The organization of prefrontal corticostriatal projections to the core or shell of the nucleus accumbens has been studied in great detail in rodents by means of retrograde and anterograde tracing methods. The main prefrontal cortical inputs to the medial and lateral shell of the rat accumbens arise from the dorsal peduncular and infralimbic cortices, whereas the dorsal and ventral prelimbic and anterior cingulate cortices innervate preferentially the core. In addition, the lateral shell also receives strong cortical inputs from the agranular insular, perirhinal, rostral piriform, and lateral entorhinal cortices. On the other hand, additional cortical inputs to the medial shell arise from the caudal piriform cortex as well as the lateral and medial parts of the entorhinal cortex, whereas the core is preferentially targeted by inputs from the agranular insular and perirhinal cortices *(50,51)*.

Cortical inputs to the accumbens target preferentially the spines of striatal output neurons. Direct synaptic convergence of prefrontal inputs with dopaminergic terminals and hippocampal afferents have been demonstrated *(52–54)*, which provide a solid anatomical substrate for the gating properties of hippocampal projection on prefrontal cortical inputs in the rat accumbens *(5)*.

7.2. The Amygdalostrial Projection

In primates, the amygdalostriatal projection arises preferentially from various components of the basal and accessory basal nuclear complexes *(48,55–57)*. The main striatal target of amydala projections is the ventromedial striatum. Very few, if any, amygdala inputs are sent to the central striatum. The basal and accessory basal inputs innervate both the shell and core of accumbens, except for a restricted region in the dorsomedial shell that receives few basal nucleus inputs. The projection is topographically organized so that parvicellular basal inputs terminate in ventral shell and core, whereas magnocellular inputs target ventral shell and ventromedial putamen *(48)*. The intermediate division of the basal nucleus projects broadly across the whole ventromedial striatum except the dorsomedial part of the shell. The shell also receives specific inputs from the medial part of the central nucleus and periamygdaloid cortex and additional inputs from the medial nucleus *(48,57)*.

In the rat *(51,58–60)*, the amygdalostriatal projection is much more extensive than in monkeys and involves the whole extent of the ventral and dorsal striatum except for the rostrodorsolateral part of the caudate–putamen complex. This projection is highly topographic: the rostral basolateral nucleus projects preferentially to rostral and caudolateral portions of the accumbens and large portions of the dorsal striatum, whereas the caudal basolateral nucleus projects to the rostromedial caudate–putamen complex and caudomedial portion of the nucleus accumbens.

Amygdala terminals form asymmetric synapses mainly with spines and distal dendrites of projection neurons. At the light microscopic level there is a certain degree of overlap of axons from amygdala, hippocampus, prefrontal cortex, and thalamus in

nucleus accumbens *(61,62)* and some studies suggest functional convergence of these inputs onto individual neurons *(63)*. Electron microscopic studies demonstrated synaptic convergence of amygdala inputs with dopamine terminals *(53)* and hippocampal (ventral subicular) afferents onto single striatal neurons *(64)*. These convergent inputs may possibly mediate some of the complex functional interactions disclosed between these various glutamatergic afferents to control accumbens neuronal activity.

7.3. The Hippocampostriatal Projection

In monkeys, the subiculum is the main source of hippocampal inputs to the nucleus accumbens, but additional minor inputs come from parasubiculum, prosubiculum, and CA1 and CA3 regions *(48)*. These projections, which travel through the fornix and arise predominantly from the rostral hippocampus, terminate most densely in medial and ventral portions of accumbens. There is overlap of subicular and amygdala inputs to the medial division of the nucleus accumbens, suggesting potential interactions between these two pathways to modulate information processing in the primate accumbens *(48)*.

In rats and cats, the subiculum, CA1 region, and parahippocampal cortex provide massive heterogeneous projections to the ventral striatum *(65,66)*. The ventral subiculum projects mainly to the caudomedial part of the nucleus accumbens, whereas the dorsal and septal subiculum innervate preferentially its lateral and rostral components. Hippocampal inputs converge with dopaminergic, prefrontal, and amygdala afferents at the single-cell level in the rat accumbens *(33,54,67)*.

7.4. Functional Gating of Prefrontal Cortical Inputs by Hippocampal and Amygdala Afferents to the Nucleus Accumbens

Grace and his colleagues have published a series of elegant studies over the past 5 yr that provide a solid support for tight functional interactions between cortical, amygdala, and hippocampal glutamatergic inputs within the rat nucleus accumbens *(3,5)*. In vivo, accumbens neurons exhibit a bistable steady-state membrane potential alternating from a hyperpolarized nonfiring state to a depolarized state during which neurons can fire action potentials. Inputs from the hippocampal subiculum are responsible for generating the bistable state in these neurons. If fimbria/fornix is transected, none of striatal neurons exhibit the bistable membrane potential *(5,68,69)*. Prefrontal cortical stimulation induces only brief excitatory responses that, by themselves, are unlikely to result in action potentials in accumbens neurons. However, if hippocampal inputs are stimulated first, subsequent stimulation of prefrontal cortical afferents generate action potentials in accumbens neurons *(5,68)*. Activation of the subicular inputs cause the cells to shift to a depolarized state under which conditions prefrontal inputs can generate spike discharges. The hippocampal input, therefore, appears to act as a gate for prefrontal cortical influences to accumbens neurons *(5)*. Once this gate is opened, it allows prefrontal cortical inputs to get through and activates striatal neurons. This interaction is modulated by drugs that affect dopamine transmission because such compounds have an effect on the bistable state frequency of striatal neurons. For instance, systemic injection of D1 and D2 agonists decrease the frequency at which the membrane potential of striatal neurons exhibit depolarized states. Because the depolarized state is necessary for the gating of prefrontal cortical inputs by hippocampal afferents, the effects of prefrontal cortical inputs on striatal neurons are attenuated under these conditions *(5,70)*.

Amygdala inputs also appear to gate prefrontal cortical excitatory afferents to accumbens neurons. Stimulation of amygdala induces a brief depolarization of striatal neurons. If a

stimulus from amygdala is delivered before stimulation of the prefrontal cortex, there is facilitation of prefrontal cortical inputs to induce action potential in striatal neurons. This potentiation depends on the delay between the two stimuli. The amygdala has to be activated 7–30 ms before prefrontal cortical stimulation to mediate the potentiating effects. Inputs from both the amygdala and hippocampus are, therefore, capable of gating prefrontal cortical throughput to the accumbens, but in the case of amygdala, the response is brief and likely represents a phenomenon-related event *(5)*. It is important to note that there are reciprocal functional relationships between the amygdala and the prefrontal cortex; that is, prefrontal cortical stimulation influences neuronal activity in the amygdala and vice versa. Interestingly, cortical stimulation exerts inhibitory influences on the amygdala. This inhibitory effect appears to be mediated through various mechanisms that recruit amygdala GABAergic interneurons including a chloride-mediated hyperpolarization, persistent decrease in neuronal inputs resistance, and shunting of postsynaptic potentials *(71)*. Dopamine appears to be an important modulator of this functional interplay between the prefrontal cortex and amygdala *(71)*.

Although the exact functions of these gates are not clearly defined, Grace and colleagues have hypothesized that the hippocampal subiculum inputs may gate context-related events, whereas the amygdala may be involved in modulating prefrontal cortical stimuli related to emotion or affective states. Given the fact that schizophrenics show deficits in tasks that contain context-related information, one may hypothesize that a primary pathology of these brains relies upon the malfunctioning of the hippocampal gate of prefrontal cortical information at the level of the nucleus accumbens *(3,5)*.

8. CONCLUDING REMARKS

The importance of glutamatergic transmission in psychiatric diseases is now well established. Although much emphasis has been devoted to the prefrontal cortex, data presented in this review highlight the importance of other glutamatergic pathways from the amygdala and hippocampus. The complex functional interactions between these glutamatergic afferents to the nucleus accumbens, combined with the direct and indirect modulation these glutamatergic brain structures may exert on the activity of midbrain dopaminergic neurons, emphasize the importance of a tight balance of activity between glutamatergic and dopaminergic transmission to the prefrontal cortex and the nucleus accumbens for normal integration and processing of cognitive and limbic information. A shift in that balance leading to an increase release of dopamine at cortical and subcortical levels may be a critical factor that underlies the appearance, maintenance, and relapse of psychiatric diseases in humans.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health and the US Army.

REFERENCES

1. Weickert CS, Kleinman JE. The neuroanatomy and neurochemistry of schizophrenia. Psychiatr Clin North Am 1998; 21:57–75.
2. Carlsson A, Waters N, Carlsson ML. Neurotransmitter interactions in schizophrenia—therapeutic implications. Biol Psychiatry 1999; 46:1388–1395.

3. Moore H, West AR, Grace AA. The regulation of forebrain dopamine transmission: relevance to the pathophysiology and psychopathology of schizophrenia. Biol Psychiatry 1999; 46:40–55.
4. Benes FM. Emerging principles of altered neural circuitry in schizophrenia. Brain Res Rev 2000; 31:251–269.
5. Grace AA. Gating of information flow within the limbic system and the pathophysiology of schizophrenia. Brain Res Rev 2000; 31:330–341.
6. Lewis DA, Gonzalez-Burgos G. Intrinsic excitatory connections in the prefrontal cortex and the pathophysiology of schizophrenia. Brain Res Bull 2000; 52:309–317.
7. Meador-Woodruff JH, Healy DJ. Glutamate receptor expression in schizophrenic brain. Brain Res Rev 2000; 31:288–294.
8. Rajkowska G. Histopathology of the prefrontal cortex in major depression: what does it tell us about dysfunctional monoaminergic circuits? Prog Brain Res 2000; 126:397–412.
9. Terenius L. Schizophrenia: pathophysiological mechanisms—a synthesis. Brain Res Rev 2000; 31:401–404.
10. Hoffman RE, McGlashan TH. Neural network models of schizophrenia. Neuroscientist 2001; 7:441–454.
11. Sharp FR, Tomitaka M, Bernaudin M, Tomita. Psychosis: pathological activation of limbic thalamocortical circuits by psychomimetics and schizophrenia? Trends Neurosci 2001; 330–334.
12. Moghaddam B. Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders. Biol Psychiatry 2002; 51:775–787.
13. Pralong E, Magistretti P, Stoop R. Cellular perspectives on the glutamate-monoamine interactions in limbic lobe structures and their relevance for some psychiatric disorders. Prog Neurobiol 2002; 67:173–202.
14. Frankle WG, Lerma J, Laruelle M. The synaptic hypothesis of schizophrenia. Neuron 2003; 39:205–216.
15. Spedding M, Neau I, Harsing L. Brain plasticity and pathology in psychiatric disease: sites of action for potential therapy. Curr Opin Pharmacol 2003; 3:33–40.
16. Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol Psychiatry 1999; 45:17–25.
17. Carmichael ST, Price JL. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. J Comp Neurol 1994; 346:366–402.
18. Goldman-Rakic PS. Anatomical and functional circuits in prefrontal cortex of nonhuman primates. Relevance to epilepsy. Adv Neurol 1995; 66:51–63.
19. Goldman-Rakic PS. The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. Biol Psychiatry 1999; 46:650–661.
20. Preuss TM, Goldman-Rakic PS. Crossed corticothalamic and thalamocortical connections of macaque prefrontal cortex. J Comp Neurol 1987; 257:269–281.
21. Romanski LM, Giguere M, Bates JF, Goldman-Rakic PS. Topographic organization of medial pulvinar connections with the prefrontal cortex in the rhesus monkey. J Comp Neurol 1997; 379:313–332.
22. Giguere M, Goldman-Rakic PS. Mediodorsal nucleus: areal, laminar, and tangential distribution of afferents and efferents in the frontal lobe of rhesus monkeys. J Comp Neurol 1988; 277:195–213.
23. Pakkenberg B. Total nerve cell number in neocortex of schizophrenics and controls estimated using optical dissectors. Biol Psychiatry 1993; 34:768–772.
24. Young KA, Manaye KF, Liang C, Hicks PB, German DC. Reduced number of mediodorsal and anterior thalamic neurons in schizophrenia. Biol Psychiatry 2000; 47:944–953.
25. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch Gen Psychiatry 2000; 57:65–73.

26. Lewis DA, Cruz DA, Melchitzky DS, Pierri JN. Lamina-specific deficits in parvalbumin-immunoreactive varicosities in the prefrontal cortex of subjects with schizophrenia: evidence for fewer projections from the thalamus. Am J Psychiatry 2001; 158:1411–1422.
27. Volk DW, Pierri JN, Fritschy JM, Auh S, Sampson AR, Lewis DA. Reciprocal alterations in pre- and postsynaptic inhibitory markers at chandelier cell inputs to pyramidal neurons in schizophrenia. Cereb Cortex 2002; 12:1063–1070.
28. Volk DW, Lewis DA. Impaired prefrontal inhibition in schizophrenia: relevance for cognitive dysfunction. Physiol Behav 2002; 77:501–505.
29. Volk DW, Lewis DA. Effects of a mediodorsal thalamus lesion on prefrontal inhibitory circuitry: implications for schizophrenia. Biol Psychiatry 2003; 53:385–389.
30. Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: burst firing. J Neurosci 1984: 4:2877–2890.
31. Murase S, Grenhoff J, Chouvet G, Gonon FG, Svensson TH. Prefrontal cortex regulates burst firing and transmitter release in rat mesolimbic dopamine neurons studied in vivo. Neurosci Lett 1993; 157:53–56.
32. Smith Y, Charara A, Parent A. Synaptic innervation of midbrain dopaminergic neurons by glutamate-enriched terminals in the squirrel monkey. J Comp Neurol 1996; 364:231–253.
33. Sesack SR, Pickel VM. Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. J Comp Neurol 1992; 320:145–160.
34. Smith ID, Grace AA. Role of the subthalamic nucleus in the regulation of nigral dopamine neuron activity. Synapse 1992; 12:287–303
35. Charara A, Smith Y, Parent A. Glutamatergic inputs from the pedunculopontine nucleus to midbrain dopaminergic neurons in primates: *Phaseolus vulgaris*-leucoagglutinin anterograde labeling combined with postembedding glutamate and GABA immunohistochemistry. J Comp Neurol 1996; 364:254–266.
36. Carr DB, Sesack SR. Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. J Neurosci 2000; 20:3864–3873.
37. Groenewegen HJ, Wright CI, Beijer AV. The nucleus accumbens: gateway for limbic structures to reach the motor system? Progr Brain Res 1996; 107:485–511.
38. Heimer L. Basal forebrain in the context of schizophrenia. Brain Res Rev 2000; 31:205–235.
39. Fudge JL, Haber SN. The central nucleus of the amygdala projection to dopamine subpopulations in primates. Neuroscience 2000; 97:479–494.
40. Fudge JL, Haber SN. Bed nucleus of the stria terminalis and extended amygdala inputs to dopamine subpopulations in primates. Neuroscience 2001; 104:807–827.
41. Yeterian EH, Van Hoesen GW. Cortico-striate projections in the rhesus monkey: the organization of certain cortico-caudate connections. Brain Res 1978; 139:43–63.
42. Yeterian EH, Pandya DN. Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. J Comp Neurol 1991; 312:43–67.
43. Kunishio K, Haber SN. Primate cingulostriatal projection: limbic striatal versus sensorimotor striatal input. J Comp Neurol 1994; 350:337–356.
44. Haber SN, Kunishio K, Mizobuchi, Lynd-Balta E. The orbital and medial prefrontal circuit through the basal ganglia. J Neurosci 1995; 15:4851–4867.
45. Price JL, Carmichael ST, Drevets WC. Networks related to the orbitral and medial prefrontal cortex: a substrate for emotional behavior? Progr Brain Res 1996; 107:523–536.
46. Ferry AT, Ongur D, An X, Price JL. Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks. J Comp Neurol 2000; 425:447–470.
47. Yeterian EH, Pandya DN. Corticostriatal connections of the superior temporal region in rhesus monkeys. J Comp Neurol 1998; 399:384–402.

48. Friedman DP, Aggleton JP, Saunders RC. Comparison of hippocampal, amygdala, and perirhinal projections to the nucleus accumbens: combined anterograde and retrograde tracing study in the macaque brain. J Comp Neurol 2002; 450:345–365.
49. Selemon LD, Goldman-Rakic PS. Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. J Neurosci 1985; 5:776–794.
50. Berendse HW, Galis-de Graaf Y, Groenewegen HJ. Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat. J Comp Neurol 1992; 316:314–347.
51. Brog JS, Salyapongse A, Deutch AY, Zahm DS. The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. J Comp Neurol 1993; 338:255–278.
52. Sesack SR, Pickel VM. In the rat nucleus accumbens, hippocampal and catecholaminergic terminals converge on spiny neurons and are in apposition to each other. Brain Res 1990; 527:266–279.
53. Johnson LR, Aylwards RL, Hussain Z, Totterdell S. Input from the amygdala to the rat nucleus accumbens: its relationship with tyrosine hydroxylase immunoreactivity and identified neurons. Neuroscience 1994; 61:851–865.
54. French SJ, Totterdell S. Hippocampal and prefrontal cortical inputs monosynaptically converge with individual projection neurons of the nucleus accumbens. J Comp Neurol 2002; 446:151–165.
55. Smith Y, Parent A. Differential connections of caudate nucleus and putamen in the squirrel monkey (*Saimiri sciureus*). Neuroscience 1986; 18:347–371.
56. Russchen FT, Bakst I, Amaral DG, Price JL. The amygdalostriatal projections in the monkey. An anterograde tracing study. Brain Res 1985; 329:241–257.
57. Fudge JL, Kunishio K, Walsh P, Richard C, Haber SN. Amygdaloid projections to ventromedial striatal subterritories in the primate. Neuroscience 2002; 110:257–275.
58. Kita H, Kitai ST. Amygdaloid projections to the frontal cortex and the striatum in the rat. J Comp Neurol 1990; 298:40–49.
59. Russchen FT, Price JL. Amygdalostriatal projections in the rat. Topographical organization and fiber morphology shown using the lectin PHA-L as an anterograde tracer. Neurosci Lett 1984; 47:15–22.
60. Wright CI, Beijer AVJ, Groenewegen HJ. Basal amygdaloid complex afferents to the rat nucleus accumbens are compartmentally organized. J Neurosci 1996; 16:1877–1893.
61. Wright CI, Groenewegen HJ. Patterns of convergence and segregation in the medial nucleus accumbens of the rat: relationships of prefrontal, cortical, midline thalamic, and basal amygdaloid afferents. J Comp Neurol 1995; 361:383–403.
62. Wright CI, Groenewegen HJ. Patterns of overlap and segregation between insular cortical, intermediodorsal thalamic and basal amygdaloid afferents in the nucleus accumbens of the rat. Neuroscience 1996; 73:359–373.
63. Finch DM. Neurophysiology of converging synaptic inputs from the rat prefrontal cortex, amygdala, midline thalamus, and hippocampal formation onto single neurons of the caudate/putamen and nucleus accumbens. Hippocampus 1996; 6:495–512.
64. French SJ, Totterdell S. Individual nucleus accumbens-projection neurons receive both basolateral amygdala and ventral subicular afferents in rats. Neuroscience 2003; 119:19–31.
65. Kelley AE, Domesick VB. The distribution of the projection from the hippocampal formation to the nucleus accumbens in the rat: an anterograde- and retrograde-horseradish peroxidase study. Neuroscience 1982; 7:2321–2335.
66. Groenewegen HJ, Room P, Witter MP, Lohman AHM. Cortical afferents of the nucleus accumbens in the cat, studied with anterograde and retrograde transport techniques. Neuroscience 1982; 7:977–995.
67. Totterdell S, Smith AD. Convergence of hippocampal and dopaminergic inputs onto identified neurons in the nucleus accumbens of the rat. J Chem Neuroanat 1989; 2: 285–298.

68. O'Donnell P, Grace AA. Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. J Neurosci 1995; 15:3622–3639.
69. O'Donnell P. Ensemble coding in the nucleus accumbens. Psychobiology 1999; 27:187–197.
70. O'Donnell P, Grace AA. Hippocampal gating of cortical throughput in the nucleus accumbens: modulation by dopamine. Biol Psychiatry 1996; 39:632.
71. Rosenkranz JA, Grace AA. Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons in vivo. J Neurosci 2002; 22:324–337.