

Dysfunctions in Multiple Interrelated Systems as the Neurobiological Bases of Schizophrenic Symptom Clusters

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Abstract

The absence of an animal model that accurately approximates schizophrenia limits current research into the pathophysiology of this disorder. Obviously, the cognitive disturbances associated with schizophrenia are difficult to evaluate in laboratory animals. Nonetheless, animal studies have provided insight into the anatomy and physiology of the brain systems that have been implicated in schizophrenia. These studies also suggest how brain systems may be involved in information processing in normal and pathological conditions. Thus, a careful assessment of the properties and functions of the brain regions suggested to be involved in schizophrenic symptoms has been a primary objective in several laboratories. In this review, we discuss the interactions among the brain regions implicated in schizophrenia—the ventral striatum, prefrontal cortex, hippocampus, and dopamine systems—and provide an integrative model linking altered function in these regions with specific clusters of symptoms of schizophrenia.

Key words: Nucleus accumbens, hippocampus, prefrontal cortex, thalamus, dopamine, negative symptoms, positive symptoms, thought disorder.

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Schizophrenia is a complex disorder characterized by a profound disturbance of cognitive functions. A major problem in the study of schizophrenia is the diversity of its symptoms, leading to the suggestion that schizophrenia is actually a cluster of diseases. An integrative clinical view was brought up by Liddle, who used factor analysis to segregate symptoms of schizophrenia into three clusters—reality distortion, psychomotor poverty, and disorganization (Liddle et al. 1992*b*)—and proposed that dysfunctions in specific brain regions were involved in each cluster of symptoms (Liddle et al. 1992*a*, 1992*b*). This

interpretation is reinforced by a number of studies that implicate a variety of structures in the pathophysiology of schizophrenia. These structures include the prefrontal cortex (PFC), medial temporal lobe (including the hippocampus), ventral striatum, and mesolimbic dopamine (DA) system. In this review, we will link information regarding the physiological interactions among these systems with clinical investigations, in an attempt to analyze these symptom clusters from an anatomical perspective.

DA Systems in Schizophrenia

The involvement of DA in schizophrenia is supported by a long history of DA research. Pharmacological evidence suggests the presence of DA hyperactivity in schizophrenia, since clinically effective drugs are DA antagonists (Carlsson and Lindqvist 1963; Matthysse 1973), and their clinical efficacy correlates with their affinity for D₂ receptors (Creese et al. 1976; Seeman 1987). Also, treating Parkinson's disease with the DA precursor L-dopa may result in psychosis as a side effect (Jenkins and Groh 1970), and the DA agonist amphetamine is known to induce psychotic states (Angrist et al. 1971, 1974; Snyder 1972). However, an actual increase in DA levels or DA turnover could not be demonstrated in the schizophrenic brain (Post et al. 1975; van Kammen et al. 1986; Beuger et al. 1996), and alterations in DA receptor binding have not been observed consistently (Owen et al. 1981; Martinot et al. 1991; Knable et al. 1994). In fact, some studies have actually shown a decreased DA turnover (van Kammen et al. 1986; Heritch 1990; Kahn et al. 1994; Rao and Möller 1994) and have raised the possibility of a hypoactive DA system involvement in this disorder. Furthermore, Angrist et al. (1980, 1982; Sanfilipo et al. 1996) demonstrated that DA agonists may improve at least a subset of the symptoms

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in a group of schizophrenia patients, and it has also been reported that amphetamine improves neuropsychological performance in some schizophrenia patients (Goldberg et al. 1991). As a consequence, the role of DA in schizophrenia is more complex than a simple increase or decrease in levels of this transmitter.

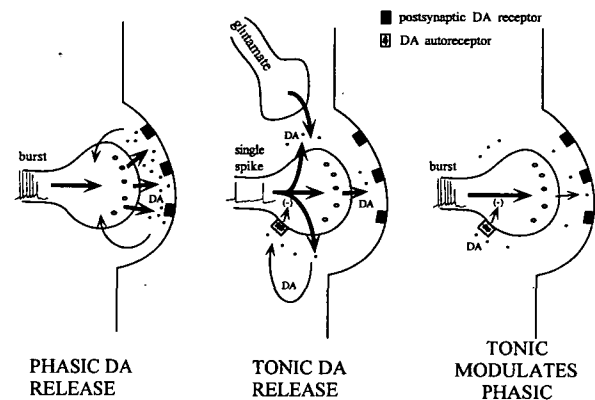
Integrative Roles of DA and Cortex in Schizophrenia

The complex regulation of DA release may account for at least some of the observations related to both increased and decreased DA activity measures in patients with schizophrenia. Indeed, researchers have proposed that DA release in striatal regions occurs via two different mechanisms (Grace 1991): a phasic DA release dependent on excitation of DA cell firing, and a basal, tonic DA release regulated by glutamatergic inputs to this region. Some authors have proposed that the activity of subcortical DA systems can be affected by hypofrontality (Weinberger et al. 1988) or hippocampal deficiencies (Lipska et al. 1992; Bardgett et al. 1995). Thus, a decrease in glutamatergic input to the nucleus accumbens, due to either prefrontal or hippocampal disturbances, may eventually result in a reduced tonic DA release. This may reduce the activation of DA autoreceptors that regulate the release of phasic DA (Grace 1991, 1992). Therefore, as a consequence of a cortical deficit, basal extracellular levels of DA may be reduced, leading to a lower level of inhibition of DA release by presynaptic DA autoreceptors. When bursts of action potentials reach the DA terminal, the amount of DA phasically released will increase due to the absence of this local autoregulatory suppressive mechanism. Thus, a reduced tonic DA activity may coexist with an increased spike-dependent DA release (figure 1).

Cortical Disturbances in Schizophrenia

Prefrontal cortical dysfunction has been consistently found in schizophrenia patients. Some magnetic resonance imaging (MRI) studies have found a decrease in prefrontal cortical volume (Harvey et al. 1993; Andreasen et al. 1994b). Postmortem studies show that schizophrenia patients exhibit alterations in cytoarchitecture of the dorsolateral PFC (Daviss and Lewis 1995; Selemon et al. 1995), a loss of glutamate receptor binding (Kerwin et al. 1990; Ulas and Cotman 1993), and a decrease in DA fibers in the PFC (Akil and Lewis 1996). From a clinical perspective, many symptoms of schizophrenia resemble those that occur as a result of a lesion in the PFC (Buchanan et al. 1994). Indeed, schizophrenia patients commit perseverative errors in a PFC-sensitive test such

Figure 1. Decreased tonic dopamine (DA) release may result in an increased spike-dependent DA release



Left: In this model, phasic DA release is proposed to occur as a result of a behaviorally relevant stimulus causing DA cells to emit a burst of spikes (Schultz 1986). Bursts of spikes arriving from the DA cell body result in fast, phasic release of DA into the synaptic cleft (thick arrows). Following stimulation of postsynaptic DA receptors, the majority of DA released in this manner is rapidly inactivated by reuptake before it can leave the synaptic cleft (curved arrows). Center: In the basal firing state, DA cells exhibit a spontaneous spike discharge in the form of single spikes, resulting in a constant low level of DA release. In this model, DA is proposed to be released primarily into the extrasynaptic space; this tonic DA release is under the control of glutamatergic afferents. The resultant elevation in extracellular DA is sufficient to activate autoreceptors on DA terminals (thin arrow). Right: The increase in tonic extracellular DA levels is proposed to reduce the phasic release of DA that occurs in response to stimulus-dependent burst firing (Grace 1991, 1992).

as the Wisconsin Card Sorting Test (WCST; Fey 1951), in which they fail despite repeated trials (Goldberg et al. 1987). Although some studies using positron emission tomography (PET) showed no alteration in basal regional cerebral blood flow (rCBF) in the PFC (Kawasaki et al. 1992), hypofrontality in schizophrenia can be observed as an absence of increase in rCBF during the WCST (Berman et al. 1986) and as an impaired functional MRI activation in verbal fluency tasks (Yurgelun-Todd et al. 1996b). Alterations in phosphomonoesters (Pettegrew et al. 1991) and *N*-acetyl aspartate (Buckley et al. 1994) in magnetic resonance spectroscopy (MRS) studies provide further evidence for prefrontal cortical dysfunction. Whether there is an anatomical disturbance of the PFC or not, this region clearly has an impaired ability to engage in its normal function in schizophrenia.

In addition to hypofrontality, studies have shown anatomical disturbances in other brain regions. Although these results have not always been replicated (Altschuler et al. 1987; Christison et al. 1989; but see Conrad et al. 1991), researchers commonly find a disruption in the spatial organization of cells in the medial temporal lobe, par-

ticularly the hippocampus (Kovelman and Scheibel 1984; Falkai and Bogerts 1986; Conrad and Scheibel 1987). Also, postmortem studies showed smaller hippocampi in schizophrenia patients (Bogerts et al. 1985), and MRI studies revealed smaller medial temporal lobes in schizophrenic brains (Barta et al. 1990; Suddath et al. 1990; Shenton et al. 1992; Bogerts et al. 1993; Gur and Pearlson 1993; Kawasaki et al. 1993b; Marsh et al. 1994; Rossi et al. 1994). Abnormal asymmetrical synapses were found in an electron microscopic study of temporal cortices obtained from schizophrenia patients (Ong and Garey 1993). MRS studies noted a loss of neuronal integrity in the schizophrenic temporal lobe, as suggested by a reduction in *N*-acetyl aspartate (Nasrallah et al. 1994; Yurgelun-Todd et al. 1996a). These findings strongly support the presence of a hippocampal disturbance in schizophrenia.

The concepts of hypofrontality and hippocampal deficit are not necessarily in opposition, as they may be indicative of a functional relationship between these structures. Indeed, in MRI studies of monozygotic twins discordant for schizophrenia, the affected twin almost invariably exhibits smaller hippocampi (Suddath et al. 1990); this reduced size of the hippocampus strongly correlates with a decreased rCBF in the PFC and a poorer performance on the WCST in the affected twin (Weinberger et al. 1992). Other brain regions reported as abnormal in schizophrenia include the amygdala (Bogerts et al. 1985; Arnold et al. 1991; Shenton et al. 1992; Marsh et al. 1994; Rossi et al. 1994), entorhinal cortex (Arnold et al. 1991; Honer et al. 1996), cingulate cortex (Benes et al. 1986, 1992; see Olney and Farber 1995 for review), planum temporale (Falkai et al. 1995; Perry et al. 1995), mediodorsal thalamic nucleus (Pakkenberg 1990, 1992; Andreasen et al. 1994a), and nucleus accumbens (Pakkenberg 1990, 1993). It is interesting that each of these structures exhibits efferent projections to either the PFC or the nucleus accumbens, or both.

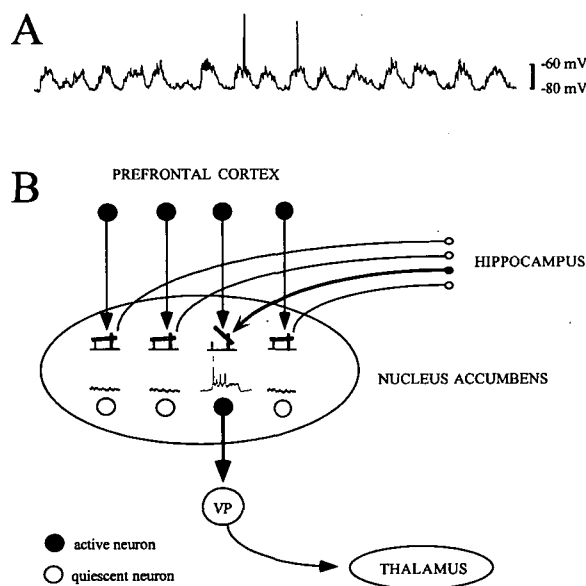
Nucleus Accumbens as an Information Integrator

Cortical deficits may have a significant impact on the function of subcortical structures. In particular, the nucleus accumbens is a brain area in which the cortical regions mentioned above may interact with DA systems. Studies suggest that this striatal region functions at the level of a motor-limbic interface (Mogenson et al. 1980) and that it is involved in schizophrenia. Indeed, the nucleus accumbens has a unique set of input connections, in that it receives afferents from virtually every brain region that has been implicated in schizophrenia. Thus, accumbens neurons receive convergent inputs from the hippocampus,

PFC, and amygdala (O'Donnell and Grace 1995b), in addition to exhibiting one of the densest dopaminergic innervations of the brain (Johansson and Hökfelt 1981).

In vivo intracellular recordings have shown that most neurons in the nucleus accumbens exhibit a bistable membrane potential, characterized by a very negative resting state that is periodically (i.e., at approximately 1 hertz) interrupted by depolarizing events lasting 100 to 500 ms (O'Donnell and Grace 1995b). It is only during these events, referred to as the active state of bistable neurons, that the cells can fire action potentials either spontaneously or in response to cortical afferent stimulation (figure 2A). These depolarizations are mediated by synaptic activation rather than being endogenously generated, as suggested by their absence during in vitro intracellular recordings (O'Donnell and Grace 1993b). Indeed, evidence shows that the hippocampal afferents to the nucleus

Figure 2. Integration of hippocampal and prefrontal cortical input in the nucleus accumbens affects information flow through this region



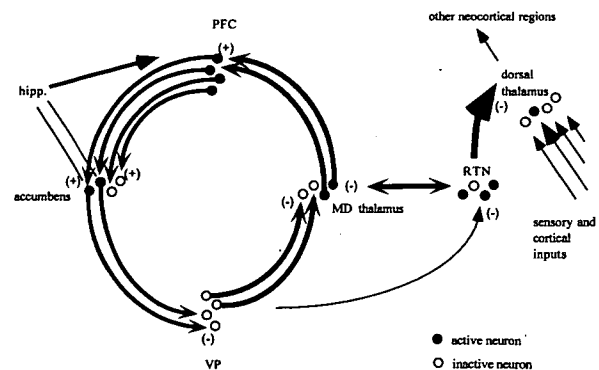
A: In vivo intracellular recordings from nucleus accumbens neurons show a membrane potential alternating between a very negative baseline with an absence of spike firing interrupted by depolarized plateaus lasting a few hundred milliseconds during which the cell can reach threshold for firing action potentials. These events are dependent on hippocampal input to the accumbens. B: This hippocampal input gates the flow of cortical information through the nucleus accumbens. Information in the form of spike firing arises from neurons in the prefrontal cortex (circles), providing inputs to neurons in the nucleus accumbens. Only those cells in the nucleus accumbens that are in the active state (gate open) as a consequence of hippocampal input (thick arrow) will fire action potentials in response to cortical afferent stimulation, thereby activating the projections of those neurons to the ventral pallidum (VP) and passing information onto the thalamus.

accumbens are responsible for the transitions to the depolarized membrane potential plateaus. Stimulation of the hippocampal afferents within the fornix induces a switch to the depolarized state in bistable accumbens neurons (O'Donnell and Grace 1995b). The spontaneous depolarizations are also dependent on hippocampal input, since they could not be detected following a transection of the fornix, and injection of the local anesthetic lidocaine into this bundle results in a temporary suppression of depolarized events in bistable cells (O'Donnell and Grace 1995b).

This modulation of the bistable membrane potential of accumbens neurons is involved in the control of the information flow through the nucleus accumbens. PFC afferent stimulation results in spike firing only when the neuron is in the depolarized state, occurring either spontaneously or in response to hippocampal afferent stimulation (O'Donnell and Grace 1995b). As a result, the input from the hippocampus, a context-sensitive structure (Jarrard 1995), can be viewed as gating the throughput of cortical information in the nucleus accumbens (figure 2B). This interaction will have a significant impact on PFC activity, since the accumbens serves as a link within cortico-subcortico-cortical circuits that provide feedback to the PFC via the ventral pallidum and mediodorsal thalamic nucleus (Parent and Hazrati 1995; O'Donnell et al. 1997). Activation of accumbens neurons disinhibits thalamocortical projections to the PFC. Thus, the modulation of the flow of PFC information through the accumbens affects which units in the PFC receive feedback activation through this circuit, according to the context imposed by the hippocampal afferents to the accumbens (figure 3).

The flow of cortical information through the nucleus accumbens can also be modulated via lateral interactions between accumbens neurons. Striatal medium spiny neurons exhibit dye coupling (O'Donnell and Grace 1993a; Onn and Grace 1994), which is a measure of gap junction permeability. Increasing the levels of coupling may enhance integration of information via changes in the size of neuronal clusters that may be activated by hippocampal/PFC interactions. Although gap junctions may be an effective means of synchronizing the activity of otherwise inhibitory gamma-aminobutyric acid (GABA)ergic neurons, gap junctions behave as low-pass filters, optimized for transmission of slow signals (Hagiwara and Morita 1962). One possibility is that gap junctions may allow synchronization of the depolarized events constituting the active state of accumbens neurons, since these events would be much less attenuated than spike activity. If so, modulation of gap junction permeability may significantly influence the outflow of information from the nucleus accumbens and dorsal striatum back to prefrontal and cingulate cortices by setting the size of the cluster of neurons in which PFC input can induce spike activity.

Figure 3. Flow of cortical information through the nucleus accumbens has an impact on thalamocortical activity



Accumbens neurons activated by hippocampal/prefrontal cortex (PFC) interactions send inhibitory projections to the ventral pallidum (VP), which in turn disinhibits neurons in the mediodorsal (MD) thalamic nucleus that project back to the PFC. In addition, VP neurons also inhibit the reticular thalamic nucleus (RTN), which is involved in filtering the flow of sensory information in thalamocortical systems. Hippocampal (hipp.) inputs to the nucleus accumbens select those units that are appropriate to be activated in a given situation, allowing the appropriate set of PFC neurons to become reinforced via their MD afferents.

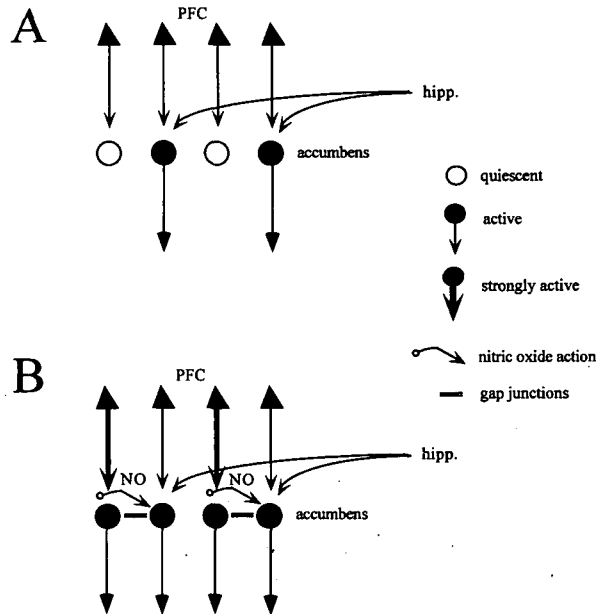
An intriguing new factor in this modulation is the ability of nitric oxide to increase gap junction permeability in the dorsal striatum (O'Donnell and Grace 1997). Since nitric oxide is thought to be released as a consequence of glutamate receptor activation (Bredt and Snyder 1989; East and Garthwaite 1991), it is possible that the cortex itself is capable of modulating cluster size within the nucleus accumbens. As a result, a particularly strong cortical activation may be capable of overriding the hippocampally driven selective gating by permitting activation of neurons beyond the context-dependent set (figure 4).

Multiple Levels of Action Exerted by DA Within the Nucleus Accumbens

The actions of DA can be analyzed at several different levels. Although these actions in the nucleus accumbens have been extensively studied, the overall nature of the actions of DA in this system is not yet fully understood. The data accumulated may in fact appear somewhat contradictory; however, they acquire consistency when analyzed in the light of the impact of DA on the flow of information within the accumbens, as opposed to trying to assign DA to a net excitatory or inhibitory role.

First, DA agonists have been shown to reduce the synaptic response of accumbens neurons to prefrontal cortical (O'Donnell and Grace 1994) and hippocampal (Yang

Figure 4. Lateral interactions via nitric oxide (NO)-activated gap junctions may affect the flow of cortical information through the nucleus accumbens



A: Active prefrontal cortex (PFC) neurons (triangles) project to discrete subsets of accumbens neurons (circles). As shown in figure 3, hippocampal (hipp.) gating selects the accumbens units that are appropriate to be activated given the context. Information flow from the PFC is thus selectively gated through these hippocampally activated accumbens cells. **B:** However, strongly active cortical afferents may induce release of NO from accumbens neurons, which should induce an increase in gap junction permeability (parallel lines between accumbens neurons). In this way, selective hippocampal gating can be overridden by strong cortical activation.

and Mogenson 1984; Pennartz et al. 1992) inputs. D_2 agonists can reduce the synaptic responses of PFC inputs to nucleus accumbens neurons; indeed, this system is sufficiently sensitive to DA that tonic levels of this neurotransmitter present extracellularly *in vitro* are sufficient to attenuate this PFC input (O'Donnell and Grace 1994). In contrast, D_1 receptor stimulation is required to reduce the effects of local stimulation-evoked excitatory postsynaptic potentials on accumbens cells (Harvey and Lacey 1996) that, extrapolating from the similar pharmacology, may be elicited by activation of hippocampal afferents (Pennartz et al. 1992). The pharmacology of these actions appears to be different from classical D_1 effects, since it does not involve activation of adenylate cyclase (Harvey and Lacey 1996) and in one report required exceedingly high doses of agonist administration (Nicola et al. 1996). Second, DA agonists decrease accumbens cell excitability at postsynaptic sites, as reflected in the amplitude of intracellular current injection necessary to evoke spike discharge (O'Donnell

and Grace 1996). This effect requires coactivation of D_1 and D_2 receptors. Third, activation of DA receptors affects the distribution of excitatory inputs and perhaps the synchronization of cell activity via modulation of gap junction permeability (O'Donnell and Grace 1993a). In the accumbens core and caudate-putamen, activation of D_1 receptors reduces gap junction permeability, whereas in the accumbens shell activation of the more sensitive D_2 receptors induces an increase in gap junction permeability (O'Donnell and Grace 1993a). Such actions will change the size of the integrator function by increasing or decreasing the number of cell assemblies functionally coupled and affecting the gating of cortical throughput in the accumbens.

Although most of these actions could be characterized as "inhibitory," it has been suggested that a DA-mediated inhibition may actually reduce the neural activity that is not relevant to the task being undertaken. Indeed, on one hand, DA is a transmitter that may diffuse away from its site of release and act via "volume transmission" (Agnati et al. 1995); on the other hand, Schultz (1994) has shown that, given a behaviorally relevant stimulus, DA cells fire en bloc. Therefore, the actions of DA resulting in a decreased flow of cortical information through the striatum are exerted over a relatively large spatial domain within this structure. As Schultz (1994) suggested, this may allow only the strongest stimuli to overcome such diffuse inhibition, with the overall action of DA being one of further limiting responses to those stimuli relevant to the current context. Indeed, stimulation of the hippocampus was shown to evoke inhibition of DA cell activity for a period consistent with the plateau depolarization of accumbens neurons, while causing a rebound in DA cell activity at the termination of this event (Harden and Grace 1995). As a result, the DA input may act in conjunction with the hippocampal input to allow greater PFC throughput during the plateau phase, and it may act in shutting down transmission at its termination. In a similar manner, it may be possible that a broad DA-mediated inhibition in the accumbens that occurs via presynaptic tonic inhibition of PFC afferents (O'Donnell and Grace 1994) may exert a similar focusing effect by allowing passage of PFC information only through those cells receiving a strong hippocampal gating.

Accumbens Output Is Also Directed to the Reticular Thalamic Nucleus

Although schizophrenia is essentially a disorder of higher cognitive functions, a link between DA in the basal ganglia and perception-related neocortical dysfunction has remained elusive for years. However, recent studies now suggest that such interactions may occur via several mecha-

nisms. A number of output pathways have been shown to project from the basal ganglia onto neocortical areas. The accumbens shell (the most limbic striatal region) has a strong projection to the medial aspect of the mediodorsal thalamic nucleus (an area with heavy interconnections with the PFC) via a disinhibitory influence on the medial ventral pallidum (O'Donnell et al. 1997). On the other hand, projections originating in the accumbens core may target different ventral pallidal outputs (Zahm et al. 1996). We have recently shown, using pseudorabies virus as a transynaptic tracer, that the accumbens core projections via the ventral pallidum to the mediodorsal-PFC are sparse and complemented with stronger projections from this region to the ventral pallidal cells innervating the reticular thalamic nucleus (RTN) (O'Donnell et al. 1997). Furthermore, electrophysiological recordings from cells in the RTN have shown that stimulation of the ventral pallidum induces inhibitory synaptic responses in the RTN (Lavín and Grace 1994). Given the role of the RTN in the regulation and filtering of thalamocortical activity, the modulation of cortical throughput within the nucleus accumbens may have a widespread impact on cortical function.

The RTN exerts tight control on thalamocortical activity by gating its activation (Steriade and Llinás 1988). Therefore, accumbens output may have an impact on RTN-thalamic activity in a way that allows it to exert control over a wide array of cortical regions (figure 2) (Lavín and Grace 1994). This view is consistent with the proposed filtering of thalamocortical activity by the RTN, a region that coordinates cortico-cortical interactions and selective activation of specific thalamocortical systems. Inhibition of the RTN would therefore disrupt the ability of the system to selectively activate appropriate thalamocortical circuits or to coordinate the progression of information flow through the cortex; for example, from primary sensory regions to higher integrative regions. A dysfunction in this system may result in a disorder in the logical flow of thought or in an inability to selectively attend to stimuli. The disturbance in cognitive performance that patients with dorsolateral PFC lesions show in the presence of distracting stimuli may relate to this dysfunction (Chao and Knight 1995). One thalamic region with heavy connections with the RTN is the anterodorsal nucleus (Lozsádi 1994; O'Donnell et al. 1997), which is the origin of thalamic projections to the cingulate cortex.

Hippocampal Gating of PFC Throughput in the Nucleus Accumbens in Schizophrenia

The interactions between PFC and hippocampal inputs to the nucleus accumbens are likely to be affected in schizo-

phrenia. A hippocampal disturbance was suggested (Sibley et al. 1982) as the site of the developmental disorder proposed to be involved in the etiology of schizophrenia (Feinberg 1982). As reviewed in the previous sections, such a disruption could readily result in secondary alterations in PFC function and in DA system malfunction. Although the hippocampus provides direct projections to the PFC (Swanson 1981), the strongest drive of PFC neuronal activity resides in its thalamic afferents. Thus, a reduction in mediodorsal thalamic activity will be likely to interfere with PFC function. Our physiological data may provide a means by which a putative primary hippocampal disturbance could result in functional hypofrontality. A hippocampal deficit will result in a reduced gating of cortical throughput in the nucleus accumbens, which will in turn lead to increased inhibition of thalamocortical activity in the mediodorsal PFC system. As a consequence, whether or not there is an anatomical disturbance, the PFC compromise will be expressed as a reduced activation of this region during performance of tasks that require its intervention (e.g., during the WCST). As a result, neuronal activation within this circuit will not be congruent with what the context requires, due to the disabled hippocampal input. In short, there will be an absence of context dependency in the processing of information, which is a characteristic deficit reported to be present in patients with schizophrenia (Chapman et al. 1964; de Silva and Hemsley 1977; Spitzer 1993).

Categories of Symptoms in Schizophrenia

It is evident that symptoms of schizophrenia encompass more than a single domain. An ideal model should account for the diversity of symptoms constituting schizophrenia. Using a factor analysis scheme, Liddle proposed a means to subdivide the symptoms of schizophrenia into three clusters that appear to be regulated independently (Liddle et al. 1992a): (1) reality distortion, generally corresponding to positive symptoms; (2) psychomotor poverty, or negative symptoms, characterized by apathy and loss of verbal fluency; and (3) disorganization, associated with attentional impairment and thought disorder.

Initial rCBF PET assessments revealed disturbed blood flow in the PFC, temporal lobe, and basal ganglia regions of patients with schizophrenia (Buchsbaum 1990). However, a clinical correlation with respect to symptom class was not sought in these studies. Further studies associated the three syndromes with specific patterns of rCBF activation and neuropsychological profiles (see below). Evidence for the involvement of cortical-subcortical inter-

actions in a model of the emergence of schizophrenic symptoms will be provided below.

Model of the Neurobiological Systems Proposed to Underlie the Three Clusters of Schizophrenia Symptoms

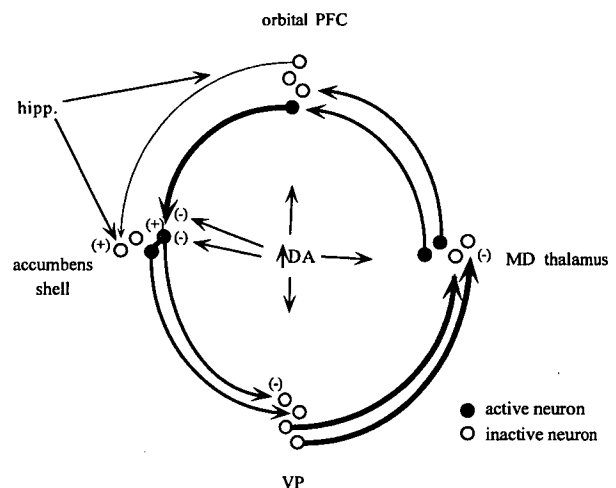
Positive Symptoms. The positive syndrome has been correlated with increased rCBF in the medial temporal lobe (Kawasaki et al. 1992; Liddle et al. 1992a, 1992b) and ventral striatum (Liddle et al. 1992b; Busatto et al. 1995) of patients with schizophrenia, and patients with prominent positive symptoms exhibit abnormal temporal lobes in MRI scans (Wible et al. 1995). Recent studies using PET scans during hallucinations revealed activation of the thalamus, putamen, accumbens, and hippocampus (Silbersweig et al. 1995), in addition to auditory cortical regions (Suzuki et al. 1993). Furthermore, because psychoses mediated by DA agonists are rich in hallucinations (Angrist et al. 1971) and amphetamine-induced hallucinations are not complemented by negative symptoms (Angrist et al. 1980), an increase in DA levels appears to be involved in the expression of positive, but not negative, symptoms. An additional line of evidence for a DA involvement in positive symptoms arises from reports that classic antipsychotic drugs, which are composed of the most potent DA antagonists, are most effective against positive symptoms but are less effective at treating negative symptoms.

The striatal region most likely to be involved in the interaction between cortical and dopaminergic systems that results in the expression of positive symptoms is the accumbens shell, since clinically active drugs (which are in general most effective against positive symptoms), when administered repeatedly, modify several functional measures of activity within this region (Deutch et al. 1992; O'Donnell and Grace 1995a). An increase in phasic DA release in the accumbens shell in schizophrenia patients would be expected to inhibit accumbens cells directly (O'Donnell and Grace 1996). Moreover, the postulated decrease in PFC-dependent tonic DA levels would decrease gap junction communication in this region (O'Donnell and Grace 1993a), which would further limit the spread of excitation in the nucleus accumbens. Under these conditions, the normal flow of information would be impaired. If any input from the PFC overcomes this state, it may cause a local increase in nitric oxide to augment gap junction communication. As a consequence, inputs that can activate accumbens cells to override the deficit in hippocampal drive are likely to stimulate inappropriate subsets of cells in this region. Thus, out-of-context information may be allowed to traverse the system, ultimately

resulting in the activation of inappropriate cortical units (figure 5). In addition to activating inappropriate neural units, the overall cell activity in the accumbens will be depressed. Decreased accumbens activity either via a decreased hippocampal input or an increased phasic DA release would lead to disinhibition of the ventral pallidum. Since the accumbens shell projects primarily to the ventral pallidal cells that project to the mediodorsal thalamic nucleus (O'Donnell et al. 1997), decreased accumbens activity would be expected to abnormally depress activity in the mediodorsal-PFC loop, leading to both hypofrontality and the emergence of positive symptoms, possibly via the orbitofrontal PFC innervation (figure 5).

Negative Symptoms. The negative syndrome has typically been associated with a state of hypofrontality, partic-

Figure 5. Positive symptoms in schizophrenia may involve abnormal flow of cortical information through the nucleus accumbens



POSITIVE SYMPTOMS

An increase in phasic dopamine (DA) activity is proposed to decrease accumbens cell excitability, whereas the decrease in tonic DA would reduce the spread of excitation in the accumbens via gap junctions. As a result, most of the prefrontal cortex (PFC) input would be ineffective at exciting neurons in the nucleus accumbens. Only those PFC inputs that are sufficiently strong (thick arrow) to overcome these barriers will excite accumbens neurons; indeed, the decrease in tonic DA inhibition of PFC terminals would potentiate any excitatory drive that arises. Thus, in spite of the hypofrontality or hippocampal (hipp.) deficit (shown as fewer arrows than in figure 3), it may still be possible for a particularly strong glutamatergic input to increase coupling to result at most in activation of a small yet inappropriate set of accumbens neurons. The overall inhibitory nature of DA on the flow of cortical information through the nucleus accumbens will also induce a global decrease in accumbens neuron activity. Such activation of inappropriate subsets of neurons in this loop in the face of abnormally low levels of mediodorsal (MD)-PFC activity could underlie hallucinatory phenomena. VP = ventral pallidum.

ularly when it affects the dorsolateral PFC. It has also been associated with altered blood flow in the caudate nucleus (Kawasaki et al. 1992; Liddle et al. 1992a, 1992b), thalamus (Tammenga et al. 1992), and dorsolateral PFC (Friston 1992; Kawasaki et al. 1992; Liddle et al. 1992a, 1992b; Wolkin et al. 1992; Batista et al. 1995). Furthermore, patients primarily showing the deficit syndrome perform more poorly in PFC-sensitive neuropsychological tests such as the WCST (Berman et al. 1986; Buchanan et al. 1994), during which they fail to exhibit the increased rCBF that normal subjects exhibit in the PFC during this task (Berman et al. 1986; Kawasaki et al. 1993a; Parellada et al. 1994). Metabolism in the dorsolateral PFC is inversely correlated with the severity of negative symptoms (Wolkin et al. 1992), and phosphomonoesters are reduced in the PFC of schizophrenia patients with high scores on negative symptoms (Shiori et al. 1994). Studies of patients with PFC lesions show a number of characteristics in common with the negative symptoms of schizophrenia (Nasrallah et al. 1981). A temporal lobe involvement in negative symptoms has also been proposed, since MRI studies revealed abnormal temporal lobe asymmetry in deficit patients (Turetsky et al. 1995).

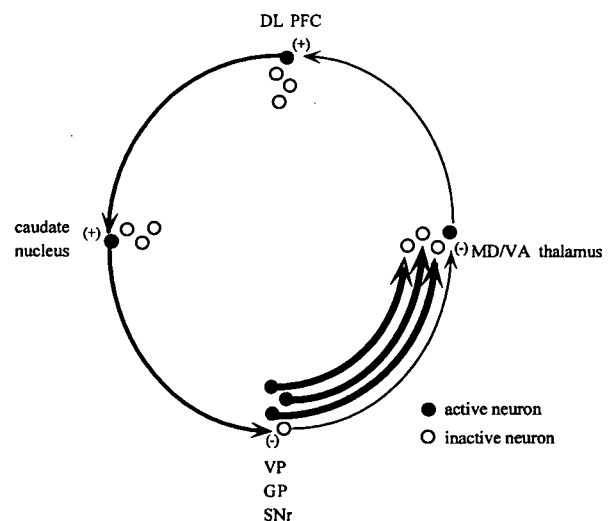
In addition, a hypoactive DA system appears to be associated with psychomotor poverty in schizophrenia. The decrease in DA turnover is more pronounced in patients with schizophrenia who have a prominent deficit syndrome (Rao and Möller 1994; Ribeyre et al. 1994). Furthermore, DA agonists have been shown to improve negative symptoms in some patients (Angrist et al. 1980, 1982; Sanfilippo et al. 1996), particularly those whose positive symptoms have been stabilized by antipsychotic drugs (Popli and Jaskiw 1995). This finding is consistent with studies showing that infusion of DA antagonists into the PFC interferes with the normal functioning of this region (Sawaguchi and Goldman-Rakic 1994), suggesting that a DA deficiency that may be present in the dorsolateral PFC could play a role in the emergence of negative symptoms. Interestingly, the dorsolateral PFC does not have its primary projections to limbic regions, but instead projects most heavily to the caudate nucleus (Uylings and van Eden 1990). The caudate is known to be involved primarily in motor functions, such as sensorimotor integration and motor planning (Alexander et al. 1986). This is consistent with the suggestion by Liddle that negative symptoms can be interpreted as arising from deficits in internal generation or planning of actions (Liddle et al. 1992b). From this perspective, deficit symptoms can to some extent be expected to be more representative of an extrapyramidal dysfunction than one primarily involving the limbic system.

The consequence of this hypofrontality would be a decrease in tonic, glutamate-dependent DA release primarily within the integrative regions of the striatum

involved in motor planning and volition. As a consequence, striatal neurons would receive less excitatory drive from the cortex, which could prevent cortical control over planned behavior and may lock the system into a highly perseverative state. In addition, a decreased cortical activation of accumbens neurons will result in a lower degree of inhibition of ventral pallidal cells, which will inhibit mediodorsal neurons that project to the dorsolateral PFC more effectively. The result may be a self-perpetuating cycle of PFC inhibition that may maintain hypofrontality (figure 6). Thus, activity in this loop would remain at very low levels unless there is an external influence leading to its activation. On the other hand, restoration of the DA input to the PFC increases activity in the corticostriatal projections. Furthermore, the potentiating effect of DA on cortical afferent excitation of striatal neurons (Levine et al. 1996) would contribute to restoration of dorsolateral PFC control over motor-planning activities, thereby reversing the psychomotor retardation characteristic of negative symptoms.

Phencyclidine (PCP) and the Induction of Positive and Negative Symptom States. This model of positive and

Figure 6. Negative symptoms in schizophrenia may involve a reduced activation of caudate nucleus neurons secondary to hypofrontality



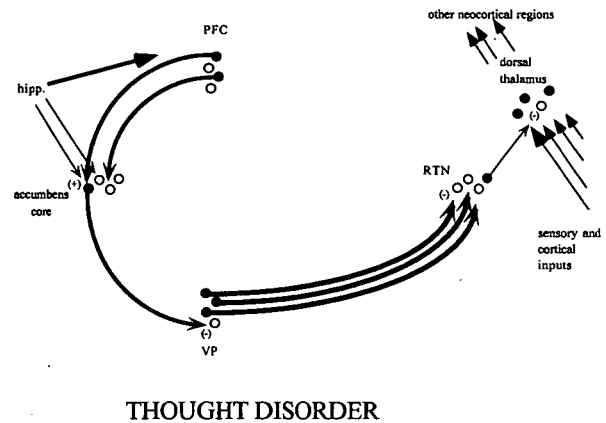
NEGATIVE SYMPTOMS

A decreased activity in the dorsolateral prefrontal cortex (DL PFC) will reduce the activity of caudate neurons; this will lead to disinhibition of the globus pallidus (GP)/ventral pallidum (VP)/substantia nigra pars reticulata (SNr) gamma-aminobutyric acid neurons and result in a stronger inhibition of mediodorsal/VA neurons. As a result, a strong input would lead to a perseverative state in the face of overall psychomotor retardation. MD/VA = mediodorsal/ventral anterior.

negative symptoms is consistent with the ability of PCP to reproduce symptoms of schizophrenia in humans. PCP is an *N*-methyl-D-aspartate (NMDA) antagonist known to induce psychotic states in normal subjects (Luby et al. 1959, 1962) and to exacerbate symptoms in schizophrenia patients (Rosenbaum et al. 1959). In schizophrenia, the contents of the PCP-induced hallucinations are similar to what the patients normally exhibit during a relapse, suggesting that PCP may be an accurate model for reproducing the positive symptoms of schizophrenia. One possible explanation for this finding is that PCP blocks NMDA receptors involved in hippocampal gating of cortical throughput in the accumbens, thereby reproducing the effects of an impaired hippocampal input to this structure. Furthermore, unlike amphetamine, PCP administration also results in the appearance of negative symptoms (Javitt and Zukin 1991). The ability of PCP to exacerbate negative symptoms could be related to its ability to mimic dorsolateral PFC dysfunction by blocking glutamatergic afferent actions within the striatum. Furthermore, since PCP is a trapped channel blocker (Honey et al. 1985) and thus requires NMDA receptor stimulation to be removed from the channel, it should have its longest duration of action at NMDA receptor channels with pathologically low levels of stimulation initially. This fact could account for both the symptom specificity and the extremely long durations of action of PCP when administered to schizophrenia patients (Javitt and Zukin 1991). Thus, PCP could gain its long duration of action in schizophrenia and its symptom specificity for both positive and negative symptoms through its ability to be "trapped" in pathologically understimulated channels within the hippocampus and its projections to the nucleus accumbens shell (positive symptoms) and in dorsolateral PFC projections to the striatum (negative symptoms).

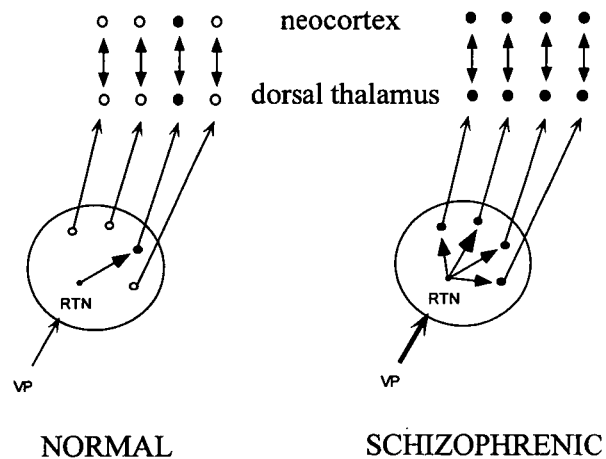
Disorganization Syndrome. The neural substrate for the disorganization syndrome is less clear. This cluster encompasses thought disorder and attentional disturbances that correlate with changes in perfusion within the cingulate cortex, mediodorsal thalamus, and ventrolateral PFC (Liddle et al. 1992a, 1992b). The disorganization syndrome is consistent with what could be predicted from a loss of regulation and coordination of activity among cortical circuits. In particular, decreased activity within the core region of the nucleus accumbens would result in increased activity of ventral pallidal cells projecting to the RTN. This activity would interfere with the ability of the RTN to selectively suppress incoming information (figures 7 and 8), since the RTN controls dorsal thalamocortical activity by filtering the information that is allowed to pass to cortical regions (Steriade and Llinás 1988). As the information entering the dorsal thalamus would not be

Figure 7. Disorganization syndrome in schizophrenia may arise from an overly inhibited reticular thalamic nucleus (RTN)



Decreased activation of the accumbens core neurons is proposed to lead to decreased activity in the RTN. Inhibition of RTN neurons would interfere with their ability to suppress thalamocortical activity, leading to a reduced filtering of inappropriate activity and aberrant, simultaneous, and unregulated activation of neocortical regions by a number of sensory and cortical inputs. VP = ventral pallidum; hipp. = hippocampal.

Figure 8. Reticular thalamic nucleus (RTN) may be involved in the disorganization syndrome of schizophrenia



Left: The RTN receives important input from the ventral pallidum (VP). In the normal situation, activation of a given set of RTN units results in the selection of specific thalamocortical projections that can be activated at a given moment while suppressing competing thalamocortical circuits. Right: In schizophrenia patients, on the other hand, the filtering function of RTN neurons is proposed to be impaired secondary to pathological levels of inhibition by the VP, resulting in inappropriate activation of several thalamocortical projections indiscriminately. This may result in aberrant information reaching cortical regions, impairing attention and interfering with the coordinated flow of thought.

attenuated, schizophrenia patients would not be able to focus on one stimulus or maintain a coherent line of thought. This mechanism could relate to the poor ability of schizophrenia patients to distinguish between relevant and irrelevant stimuli and may account for the proposed breakdown in thalamic filtering in schizophrenia (Carlsson and Carlsson 1990). Furthermore, a loss of the RTN's ability to sequentially activate selective thalamocortical systems involved in processing cortico-cortical information could also underlie the disorder in the logical flow of thought of schizophrenia patients (figure 8).

Antipsychotic Drug Treatment and DA Cell Depolarization Block

One of the strongest pieces of evidence for a DA disturbance in schizophrenia arises from the ability of D_2 receptor antagonists to alleviate schizophrenic symptoms. Antipsychotics are believed to exert their effects by inducing a change in the pattern of activity of DA cells. Thus, chronic (but not acute) administration of antipsychotic drugs results in a disturbance of the DA system that offsets the initial dysfunction. Long-term treatment with haloperidol reduces the number of active DA cells in the substantia nigra via overexcitation to the point of inactivation of spike discharge (Bunney and Grace 1978). This phenomenon is known as depolarization inactivation or depolarization block. Moreover, the clinical profile of antipsychotic drugs is highly correlated with the class of DA cells affected. Thus, treatment with classical antipsychotics results in depolarization block of DA regions that project to motor-related structures, whereas the atypical antipsychotic drug clozapine induces depolarization block in mesolimbic/mesocortical DA cells located in the ventral tegmental area (Chiodo and Bunney 1983; White and Wang 1983) that project to the limbic system.

Many research groups have provided data confirming antipsychotic drug-induced DA cell depolarization block (Skarsfeldt 1988, 1994; Henry et al. 1992; Todorova and Dimpfel 1994; see Grace et al. 1997 for review). In addition to electrophysiological data, several studies employing other techniques provided support for the ability of long-term antipsychotic drug treatment to induce depolarization block. For example, long-term haloperidol decreases DA levels in accumbens and caudate-putamen (Lane and Blaha 1987; Hernandez and Hoebel 1989; Patterson and Schenk 1991) and reduces stimulus-evoked DA release (Feasey-Truger et al. 1995). On the other hand, clozapine administration reduced basal DA release in the accumbens, but not in the dorsal striatum (Chen et al. 1991).

The presence of depolarization block in this system will have a marked impact on the flow of information

through the basal ganglia-thalamocortical systems. We have recently shown that long-term, but not acute, treatment with haloperidol or clozapine resulted in an increase in the incidence of dye coupling among accumbens shell neurons both in vitro (O'Donnell and Grace 1995a) and in vivo (Onn and Grace 1995), with a time course consistent with DA cell depolarization block (Onn and Grace 1995). This suggests that DA-modulated gap junction permeability, which may influence the processing of information within this region, can be affected by antipsychotic drug-induced depolarization block. As a consequence, a depolarization block-induced increase in coupling may allow for slow depolarizations present in these neurons to be transmitted to the coupled units. When combined with the removal of DA-mediated inhibition of accumbens cell firing, the coordinated increase in activity among coupled accumbens neurons may be sufficient to overcome a deficient excitatory hippocampal drive, and thus restore the flow of cortical throughput in the nucleus accumbens. Since this could occur without restoring hippocampal influence, only a portion of the symptoms would be affected by this type of treatment. In contrast, the ability of haloperidol, but not clozapine, to induce depolarization block in substantia nigra DA cells can be correlated with its ability to increase dye coupling among neurons in the motor-related caudate putamen. The caudate putamen does not receive substantial input from the hippocampus, and the depolarized events occurring in dorsal striatal neurons (Wilson and Kawaguchi 1996) are not dependent on hippocampal input (O'Donnell and Grace 1995b). Therefore, a depolarization block-mediated increase in gap junction permeability in this region may, instead, result in abnormal patterns of cortical activation of caudate-putamen units. Such an activation of coupling within the motor striatum may be responsible for the emergence of stereotyped motor patterns (Grace and Moore 1996) and eventually tardive dyskinesia in these patients.

Conclusion

One area of disagreement among investigators studying schizophrenia relates to whether this disorder is primarily cortical or subcortical in nature. In this review, we proposed that, independent of the location of the primary lesion, the symptoms are more likely to arise as a result of aberrant information processing in subcortical structures that ultimately results in abnormal regulation of cortical activity. We believe that this is consistent with the global deficits in information processing and cognition displayed by schizophrenia patients. In other words, widespread disruption in cortical function may readily be attributed to subcortical systems that are involved in the overall regula-

tion of thalamocortical activity, as proposed here. This contrasts with disorders that are clearly cortical in origin and expression. Thus, diseases such as Alzheimer's, focal epilepsy, or stroke tend to selectively disrupt specific functions related to their cortical loci of pathology. In contrast, regardless of the source of pathology in schizophrenia, we believe that its ultimate impact occurs via a disruption of function within subcortical systems. In this review, we have presented a hypothetical model that can account for a subcortical involvement in the higher cortical processing disturbances observed in schizophrenia. Indeed, the dependence of the interaction of basal ganglia systems with the cortex via the thalamus is consistent with the reported abnormality in thalamic volume in this disorder (Pakkenberg 1990; Andreasen et al. 1994a), conceivably due to the role of this structure as the final common pathway for interactions between the basal ganglia and the cortex

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