CHAPTER 25

Dopamine in Schizophrenia

Dysfunctional Information Processing in Basal Ganglia – Thalamocortical Split Circuits

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A. The Dopamine Hypothesis of Schizophrenia

Schizophrenia is a major mental disorder with about 0.85%–1% lifetime prevalence world wide (Jablensky et al. 1992). The course of schizophrenia is characterized by the onset of clinical symptoms after puberty and a high symptom heterogeneity. Schizophrenia symptoms are considered to fall into two major classes: positive and negative. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, the former include "distortions or exaggerations of inferential thinking (delusions), perception (hallucinations), language, and communication (disorganized speech), and behavioral monitoring (grossly disorganized or catatonic behavior)", and the latter include "restrictions in the range and intensity of emotional expression (affective flattening), in the fluency and production of thought and speech (alogia), and in the initiation of goal-directed behavior (avolition)" (pp. 274–275). While additional classifications of symptoms have been proposed (e.g., Crow 1980; Andreasen 1982; Liddle 1987; Carpenter et al. 1988, 1999; Liddle et al. 1989; Kay 1990; Buchanan and Carpenter 1994; Andreasen et al. 1995; Tandon 1995), the dopamine (DA) hypothesis of schizophrenia has been primarily related to the positive–negative classification (see below).

For about three decades, the DA hypothesis of schizophrenia has been the reigning biological hypothesis of the neural mechanisms underlying this disorder (Carlsson and Lindquist 1963; Matthysse 1973; Snyder 1973, 1974, 1976; Meltzer and Stahl 1976; Burt et al. 1977; Owen et al. 1978; McKenna 1987; Seeman 1987; Lieberman et al. 1990, 1997; Willner 1997). The DA hypothesis has undergone numerous revisions, but has proven remarkably resistant to obliteration. In its original formulation, the hypothesis stated that schizophrenia is due to a central hyperdopaminergic state. This was based on two complementary lines of indirect pharmacological evidence: the DA releaser amphetamine as well as other DA-enhancing agents such as the DA precursor L-dopa or methylphenidate, produced and exacerbated schizophrenic symptoms (Jenkins and Groh 1970; Angrist et al. 1971, 1974, 1980; Snyder 1973; Janowsky and Davis 1976; van Kammen et al. 1982; Liberman et al. 1984, 1987; Davidson et al. 1987), whereas drugs that were effective

in the treatment of amphetamine-induced psychosis and schizophrenia [neuroleptics or antipsychotic drugs (APDs)] decreased DA activity, and their clinical potency was correlated with their potency in blocking D_2 receptors (Carlsson and Lindquist 1963; Creese et al. 1976; Hyttel et al. 1985; Farde et al. 1988, 1992; Nordstrom et al. 1993).

Initially, the focus was on hyperdopaminergia in the mesostriatal DA system [DA projections from the substantia nigra pars compacta, retrorubral area and ventral tegmental area (VTA) to the neostriatum), because the neostriatum has the highest concentration of D_2 receptors in the brain, and because prolonged treatment with neuroleptics produced motor disturbances (extrapyramidal side effects), which are associated with the mesostriatal DA system (Sedvall 1996; Arnt et al. 1997; Joyce et al. 1997). Indeed, the most widely accepted definition of a neuroleptic drug had been that it has antipsychotic activity and induces extrapyramidal side effects (Arnt and Skrsfeldt 1998). In parallel, repeated high-dose amphetamine administration was deemed necessary for producing schizophrenia-like symptoms in humans (Segel 1975; Groves and Rebec 1976; Kokkinidis and Anisman 1980), and studies in rodents have revealed that the effects of comparable regimens of amphetamine administration, which led to stereotypy, are mediated by the mesostriatal DA system (Creese and Iversen 1975; Costall et al. 1977; Staton and Solomon 1984). By corollary, the most essential preclinical test of antipsychotic activity was antagonism of amphetamine-induced stereotypy in rodents (Arnt and Skarsfeldt 1998).

The first wave of challenges to the original formulation of the DA hypothesis sprung from its very cornerstones, namely, the effects of amphetamine and neuroleptic drugs, as well as from the growing recognition of the importance of negative symptoms in schizophrenia. Thus, on the one hand it became apparent that amphetamine does not produce the entire spectrum of schizophrenic symptoms but only those considered to belong to the "positive" category; moreover, it improved negative symptoms (Ogura et al. 1976; Angrist et al. 1980, 1982, 1985; Davidson et al. 1987; Daniel et al. 1990; Sanfilipo et al. 1996). On the other hand, while neuroleptics were effective in treating positive symptoms, their efficacy in treating negative symptoms turned out to be limited (Johnstone et al. 1978; Meltzer et al. 1986; 1994; Kane 1995; Breier et al. 1987; Breier and Berg 1999), and these drugs themselves could lead to a syndrome similar to the negative symptomatology of schizophrenia (Belmaker and Wald 1977; Chatterjee et al. 1995; Heinz et al. 1998). These problems were reinforced by studies of the main DA metabolite, homovanillic acid (HVA), in the cerebro-spinal fluid (CSF) and plasma of schizophrenic patients which yielded inconclusive results regarding changes in DA turnover (Post et al. 1975; van Kammen et al. 1986; Reynolds, 1989; Hsiao et al. 1993; Kahn and Davis, 1995; Beuger et al. 1996), and indeed have pointed to DA hypofunction in some schizophrenic patients (Bjerkenstedt et al. 1985; Lindstrom 1985; Wieselgren and Lindstrom 1998). Taken together, these findings have led to the proposition that positive symptoms are associated

with an increased DA function, whereas negative symptoms are associated with a decreased DA function (Meltzer 1985; Wyat 1986; Davis et al. 1991).

The postulated site of DA dysfunction has been re-conceptualized as well. The advent of the "atypical" neuroleptic clozapine, which had superior efficacy against positive as well as negative symptoms, has undermined the connection between antipsychotic efficacy and extrapyramidal side effects, as this drug had high antipsychotic efficacy at doses that did not produce extrapyramidal side effects (Hogberg et al. 1987; Arnt and Skarsfeldt 1998; Kinon and Lieberman 1996). The latter was consistent with findings that relatively to the typical APD haloperidol, clozapine produced a much weaker striatal D_2 blockade (Farde et al. 1989, 1992; Kerwin 1994; Meltzer et al. 1994; Arnt and Skarsfeldt 1998). Subsequently, a wide separation between the doses used to control psychosis and those that induce extrapyramidal side effects has become a major characteristic of the novel or "atypical" APDs (Kinon and Lieberman 1996; Arnt and Skarsfeldt 1998). Furthermore, electrophysiological, biochemical, and behavioral studies of typical and atypical APDs in rodents have revealed that clozapine and other atypical APDs exhibit selectivity for the mesolimbic DA system [originating in the VTA and terminating in the nucleus accumbens (NAC)] and reverse amphetamine-induced activity, mediated primarily by the mesolimbic DA system (Pijnenburg et al. 1975; Staton and Solomon 1984) but not stereotypy (mediated primarily by the mesostriatal DA system; Staton and Solomon 1984). In addition, Fos immunohistochemistry studies have shown that the NAC might be the common site of action of all APDs (Deutch et al. 1992; Robertson and Fibiger 1992). These findings have led to the hypothesis that antipsychotic activity is mediated by inhibition of DA function in limbic regions, whereas extrapyramidal side effects are mediated by inhibition of the mesostriatal DA function, and, by inference, that schizophrenia may be related to excessive activity in the mesolimbic DA system. As evidence has accumulated from rodent studies that the mesolimbic DA system plays a central role in complex motivational and cognitive processes (e.g., Taghzouti et al. 1985; Mogenson et al. 1988; Annett et al. 1989; Cador et al. 1989, 1991; Cole and Robbins 1989; Van den Bos and Cools 1989; LeMoal and Simon 1991; Van den Bos et al. 1991; Pennartz et al. 1994; Salamone 1994, 1997; Seamans and Phillips 1994; Ikemoto and Panksepp 1999, see also Chap. 19, this volume), and that the NAC receives, in addition to its DA input from the VTA, input from all the brain regions implicated in the pathophysiology of schizophrenia (Sesack et al. 1989; Groenewegen et al. 1990, 1991; Berendse et al. 1992, see below), the locus of the subcortical DA dysfunction in this disorder has been shifted to the mesolimbic DA system (Swerdlow and Koob 1987; Csernansky et al. 1991; Grace 1991, 1993; Gray et al. 1991; Deutch 1992; Joyce 1993, although recently, there has been a comeback of the mesostriatal system, see Graybiel 1997).

While pharmacology and results of animal studies have increasingly implicated the mesolimbic DA system, the results of neuropathological and neuroimaging studies in schizophrenia patients have increasingly pointed to a

dysfunction of cortical areas in schizophrenia. Thus, findings revealed a functional abnormality of the frontal cortex in schizophrenia ("hypofrontality", e.g., Wolkin et al. 1985, 1988, 1992; Gur et al. 1987; Volkow et al. 1987; Weinberger 1988; Weinberger et al. 1988; Berman and Weinberger 1990; Buchsbaum et al. 1990; Andreasen et al. 1992, 1996) and structural abnormalities were found in frontal and temporal brain regions in schizophrenia, including the prefrontal cortex, the entorhinal cortex, the hippocampus, and the amygdala (e.g., Kovelman and Scheibel 1984; Bogerts et al. 1985; Jakob and Beckman 1986; Bogerts 1991, 1993; Knable and Weinberger 1995; Harrison 1995, 1999; Selemon et al. 1995, 1998; Weinberger and Lipska 1995; Arnold and Trojanowski 1996; Rajkowska et al. 1998; Weickert and Weinberger 1998; Benes 1999). These findings have resurrected the proposition of Kraepelin (1919) that schizophrenia symptoms resulted from pathology of the frontal and temporal lobes, but were unrelated to the evidence of mesolimbic DA dysfunction. In addition, while the initial wave of DA hypothesis revision implied that positive and negative symptoms characterize distinct subgroups of patients, it has become clear that positive and negative symptoms coexist in schizophrenic patients (Andreasen 1982; Tandon 1995; Willner 1997). Therefore, models of schizophrenia that could link the pharmacological and neuropathological/neuroimaging lines of evidence as well as accommodate the coexistence of positive and negative symptoms have become imperative.

The formulation of such hypotheses has been made possible by the results of rodent studies which showed that: (1) the NAC is a site of convergence and interaction between the ascending mesolimbic DA system and the glutamatergic inputs from all the cortical regions whose dysfunction has been implicated in schizophrenia (Krayniak et al. 1981; Kelley and Domesik 1982; Lopes da Silva et al. 1984; Fuller et al. 1987; Groenewegen et al. 1987, 1991, 1996, 1999; Sesack et al. 1989; McDonald 1991; Brog et al. 1993; Joyce 1993; Pennartz et al. 1994; O'Donnel and Grace 1995; Finch 1996; Wright and Groenewegen 1996); and (2) perturbations of these cortical regions can modify mesolimbic DA function (Kelly and Roberts 1983; Isaacson 1984; Mogenson and Nielsen 1984; Louilot et al. 1985; Yim and Mogenson 1988; Jaskiw et al. 1990; Cador et al. 1991; Le Moal and Simon 1991; Lipska et al. 1992; Burns et al. 1993; Lipska et al. 1993; Wilkinson et al. 1993; Le Moal 1995; Karreman and Moghaddam 1996).

Two major versions of what can be termed the revised DA hypothesis have received prominence. One version, based on rodent experiments showing that the mesocortical DA system can regulate the activity of the mesolimbic DA system (e.g., Carter and Pycock 1980; Pycock et al. 1980; Louilot et al. 1989; Deutch et al. 1990; Jaskiw et al. 1991; LeMoal and Simon 1991; Deutch 1992; Rosin et al. 1992; Le Moal 1995; King et al. 1997), states that schizophrenia is associated with hypodopaminergia in the prefrontal cortex and a consequent hyperdopaminergia in the mesolimbic DA system, leading to negative and positive symptoms, respectively (Meltzer 1985; Wyat 1986; Weinberger 1987; Davis et al. 1991; Deutch 1992; Deutch et al. 1992).

The second, more general, hypothesis posits that schizophrenia reflects a dysfunction of fronto-temporolimbic-mesolimbic DA circuitry in which mesolimbic DA hyperactivity is either primary or secondary to a disrupted/reduced cortical input to the mesolimbic DA system (Frith 1987; Swerdlow and Koob 1987; Weinberger 1987; Carlsson 1988, 1995; Weinberger et al. 1988; Carlsson and Carlsson 1990; Robbins 1990, 1991; Csernansky et al. 1991; Grace 1991; Gray et al. 1991; Deutch 1992; Joyce 1993; Weinberger and Lipska 1995; O'Donnel and Grace 1998; Moore et al. 1999). Grace (1991, 1993) has advanced an influential hypothesis according to which reduced cortical input to the NAC leads to both decreased (tonic) and increased (phasic) striatal DA function leading to negative and positive symptoms, respectively (Grace 1991, 2000; O'Donnel and Grace 1998; Moore et al. 1999, see below). Csernansky et al. (1991) have proposed an additional model which combines decreased and increased striatal DA function, albeit via different mechanisms (see below).

Direct evidence for a DA dysfunction in schizophrenia has been lacking for years. As noted above, studies of HVA concentration in the CSF and in plasma have yielded inconsistent results (see Davis et al. 1991; Kahn and Davis 1995 for reviews of this literature). Early postmortem studies reported elevated levels of brain DA and DA metabolites (Bowers, 1974; Bird et al. 1977, 1979a,b,c) as well as significantly elevated numbers of D_2 receptors (Lee and Seeman 1977; Lee et al. 1978; Cross et al. 1981; Mackay 1982; Seeman et al. 1984, 1987) in schizophrenic brains. The possibility that such an increase is related to antipsychotic treatment (which has been shown in rats to elevate striatal D_2 receptors) has been contested by findings of elevated D_2 receptors in never-medicated patients (Lee et al. 1978; Owen et al. 1978; Cross et al. 1981; Farde et al. 1987). However, later studies of D_2 receptor densities in neuroleptic-naïve patients using neuroimaging techniques have yielded conflicting results (Wong et al. 1986, 1997a,b; Martinot et al. 1989, 1990, 1991; Farde et al. 1990; Tune et al. 1993, 1996; Hietala et al. 1994, Pilowsky et al. 1994; Nordstrom et al. 1995; Breier et al. 1997; Laruelle et al. 1997). Two recently published meta-analyses (Laruelle et al. 1998; Zakzanis and Hansen 1998) and several reviews (Davis et al. 1991; Soares and Innis 1999) have concluded that striatal D_2 receptor levels are moderately elevated in a substantial portion but not in all patients with schizophrenia, although Farde et al. (1995, 1997) concluded that the weight of the evidence does not point to such an elevation. Interestingly, the elevation of D_2 receptors in drug-naïve schizophrenics appears largely in the limbic region of the striatum (Mita et al. 1986; Joyce et al. 1988, 1997). In any event, it should be evident that elevation/up-regulation of D_2 receptors is not indicative of higher DA activity but rather would be in agreement with DA hypoactivity (Grace 1991; Csernansky et al. 1991).

In recent years, the development of sophisticated imaging techniques has finally allowed the demonstration of DA dysfunction in the living brain, which may with further developments become substantiated as a direct support for

the DA hypothesis. A series of studies using D_2 radioreceptor imaging have found larger displacement of the ligand from striatal D_2 receptors following amphetamine challenge in untreated and neuroleptic-naïve schizophrenics compared to healthy controls, pointing to a greater stimulation of these receptors (Laruelle et al. 1996, 1999; Breier et al. 1997; Abi-Dargham et al. 1998). Importantly, excessive DA function was found in patients who were in an active phase of the illness but not in patients in remission, suggesting that DA abnormality is not stable but is related to the clinical stage of the disease and may subserve or at least contribute to the transition to the active phase. Furthermore, amphetamine challenge and the concomitant increase in DA transmission were correlated with an exacerbation of positive symptoms and an improvement in negative symptoms, indicating that increased DA transmission is related to positive symptoms, whereas reduced DA function may be associated with negative symptoms.

Positron emission tomography (PET) studies assessing striatal DA synthesis as measured by the uptake of labeled dopa have yielded comparable findings. Thus, increased rate of DA synthesis, consistent with increased presynaptic activity, was found in both first-admission and more chronic psychotic schizophrenic patients (Hietala et al. 1994, 1995, 1999; Reith et al. 1994; Dao-Costellana et al. 1997; Hagberg et al. 1998; Lindstrom et al. 1999), whereas decreased DA synthesis appears to characterize schizophrenic patients with psychomotor slowing and depressive symptoms, i.e., primarily negative symptomatology (Hietala et al. 1995, 1999; Dao-Costellana et al. 1997).

Recently, Bertolino et al. (2000) found a selective negative correlation between a measure of neuronal integrity in dorsolateral prefrontal cortex (assessed as *N*-acetylaspartate relative concentrations measured with MRS imaging) and amphetamine-induced release of striatal DA (assessed as changes in striatal raclopride binding measured with PET) in schizophrenia patients but not in healthy controls. These results show that increased release of striatal DA after amphetamine in schizophrenia might be related to reduced glutamatergic activity of prefrontal cortex neurons, and are consistent with the hypothesis that DA dysregulation in schizophrenia may be prefrontally determined.

There have been some findings suggesting DA dysfunction in the cortex of schizophrenic patients. Using immunocytochemical methods, Akil et al. (1999) have found morphological alterations in DA axons in some areas of the prefrontal cortex, suggesting disturbance in DA neurotransmission. Lindstrom et al. (1999) have found increased uptake of L-dopa in the medial prefrontal cortex, pointing to an elevated DA synthesis. There are also some reports on receptor abnormalities in the cortex of schizophrenic subjects, including decreased density of D_1 receptors in the prefrontal cortex (Okubo et al. 1997), increased density of D_4 receptors in the entorhinal cortex (Lahti et al. 1998), and a higher (Stefanis et al. 1998) or lower (Meador-Woodruff et al. 1997) level of D_4 mRNA in the frontal cortex.

Taken together, the results obtained with the newly developed methods of neurochemical brain imaging (Soares and Innis 1999) support the DA hypothesis and moreover, suggest that hyperresponsivity of striatal DA is an important component of the positive symptomatology of schizophrenia, whereas reduced striatal DA function is involved in the pathophysiology of negative symptoms. However, the mechanisms underlying the DA abnormality remain unknown. For example, abnormal DA responsiveness to amphetamine could reflect either a presynaptic mechanism, i.e., increased DA release, or a postsynaptic mechanism, i.e., increased affinity of D_2 receptors. Another important issue relates to the basal levels of endogenously released DA in schizophrenia; thus, some authors suggested that different basal DA levels in patients may account for conflicting PET measurements of D_2 receptors (Wong et al. 1986; Farde et al. 1990, 1997), and Laruelle et al. (1999) suggested that the response to amphetamine challenge may be associated with a dysregulation of baseline DA activity. Direct measure of baseline DA levels will be necessary to unravel the nature of abnormal DA transmission in schizophrenia. Finally, due to limitations in the anatomic resolution, most imaging studies have measured the neostriatum, and the contribution of the ventral (limbic) striatum has remained largely unknown. This is a major limitation given the present emphasis on the abnormality of the mesolimbic DA system in schizophrenia. The same problem is evident with PET and single photon emission computed tomography (SPECT) studies of D_2 receptor occupancy by APDs. Only few studies exist and only for striatal D_2 receptors (Arnt and Skarsfeld 1998).

Finally, there is some evidence that D_2 receptor gene polymorphism affects susceptibility to schizophrenia (Ohara et al. 1998; Serretti et al. 1998; Jonsson et al. 1999, but see Kaneshima et al. 1997; Tallerico et al. 1999), and that allelic variation in the D_3 receptor gene may play a role in the pathophysiology of schizophrenia (Dubertret et al. 1998; Scharfetter et al. 1999, but see Malhotra et al. 1998).

B. Schizophrenia as a Dopamine-Dependent Dysfunctional Information Processing in Basal Ganglia–Thalamocortical Circuits

Several paths have been taken in attempting to link DA dysfunction to schizophrenia symptomatology. As noted above, most often DA dysfunction is related at the gross level to positive vs negative symptoms, either in a region-specific manner, e.g., hypodopaminergia of the prefrontal cortex is responsible for negative symptoms, whereas mesolimbic DA overactivity is responsible for positive symptoms (Davis et al. 1991; Meltzer 1985), or in relation to the mode of striatal DA release, i.e., increased phasic and decreased tonic release are responsible for positive and negative symptoms, respectively (Grace 1991;

O'Donnel and Grace 1998; Moore et al. 1999). Recently, it has been suggested that schizophrenia may involve a hypodopaminergic state in the dorsal striatum coupled with a hyperdopaminergic state in the ventral striatum (O'Donnel and Grace 1998; Laruelle et al. 2000), or an imbalance between modes of DA activity within the prefrontal cortex, i.e., decreased phasic and increased tonic release (Braver et al. 1999; Cohen et al. 1999).

Other approaches include the selection of a "basic" cognitive deficit which presumably underlies many schizophrenic symptoms (e.g., lack of contextual modulation; Braver et al. 1999; lack of influence of past regularities on current perception; Gray et al. 1991; disruption of working memory; Goldman-Rakic 1999), and/or endowing mesolimbic or cortical DA with a "basic" function (gain, gating, switching) whose impairment produces the schizophrenic deficit (e.g., Swerdlow and Koob 1987).

One of the major advances in the understanding of information processing in the forebrain has been the discovery that anatomically and functionally associated regions of the striatum and the frontal cortex are linked within several limbic, associative and motor basal ganglia–thalamocortical circuits (DeLong and Georgopoulos 1981; Penney and Young 1983, 1986; Alexander et al. 1986; Marsden 1986; Groenewegen and Berendse 1994; Joel and Weiner 1994; Parent and Hazrati 1995; Wise et al. 1996). Each circuit receives glutamatergic input from several separate but functionally related cortical areas, traverses specific regions of the striatum, the internal segment of the globus pallidus, substantia nigra pars reticulata (SNR), ventral pallidum and thalamus, and projects back upon a frontocortical area. Within each circuit, striatal output reaches the basal ganglia output nuclei (SNR, internal segment of globus pallidus, and ventral pallidum) via a "direct" pathway and via an "indirect pathway," which traverses the external segment of the globus pallidus and the subthalamic nucleus (DeLong et al. 1985; Penney and Young 1986; Albin et al. 1989; Alexander and Crutcher 1990; Alexander et al. 1990; Wise et al. 1996; Joel and Weiner 1997). Striatal neurons of the direct pathway contain γ-aminobutyric acid (GABA) and substance P and preferentially express D_1 receptors, while neurons of the indirect pathway contain GABA and enkephalin and preferentially express D_2 receptors (Albin et al. 1989; Gerfen et al. 1990; Reiner and Anderson 1990; Gerfen and Wilson 1996; Wise et al. 1996; Chap. 11, Vol. I). Given the preponderance of DA innervation of the striatum, it has been proposed that the understanding of the role of DA in schizophrenia might profit from an understanding of the nature of information processing within the basal ganglia–thalamocortical circuits and its modulation by DA (Frith 1987; Swerdlow and Koob 1987; Carlsson 1988; Robbins 1990; 1991; Gray et al. 1991; Graybiel 1997; Carlsson et al. 1999, 2000; Moore et al. 1999). Guided by this rationale, several "circuit models" of schizophrenia have been described. These models typically include a description of the circuit contribution to normal behavior; the modulating effect of DA on the circuit functioning; and the effects of dysfunctional DA on circuit functioning and the resulting symptomatology.

I. Circuit Models of Schizophrenia

Penney and Young (1983, 1986; Albin et al. 1989) were the first to describe how abnormalities of striatal DA disrupt the functioning of basal ganglia–thalamocortical circuitry. These authors focused on movement disorders (e.g., Parkinson's disease), and thus on the motor circuit. In their model, the direct pathway determines which sensory stimuli are used to initiate motor action, whereas the indirect pathway suppresses unwanted responses to sensory stimuli or determines which stimuli are disregarded. DA decreases the activity of striatal neurons of the indirect pathway and potentiates the activity of striatal neurons of the direct pathway. Therefore, reduced DA input to the striatum in Parkinson's disease results in underactivity of the direct pathway and overactivity of the indirect pathway, leading to reduced initiation and increased suppression of movement, manifested clinically as bradykinesia and hypokinesia.

Based on the model of Penney and Young, Swerdlow and Koob (1987) presented a circuit model of schizophrenia in which the pathophysiology of this disorder was attributed to a malfunctional limbic cortico-striato-pallido-thalamo-cortical circuit. In this circuit, the limbic striatum (NAC) selects and maintains specific sets of impulses originating in limbic structures and frontal cortex, which form the basis of emotional and cognitive processes, by inhibiting pallidal cells and thus disinhibiting the transfer of information from the thalamus to the cortex. An important component of this selection process is the sharpening of cortical information that is achieved by the dense collateral inhibitory network within the NAC. DA modulates the capacity of NAC neurons to filter out irrelevant patterns and initiate new patterns or switch existing patterns by inhibiting these neurons and thus disrupting lateral inhibition. Overactivity of DA input to the NAC results in the loss of lateral inhibition causing inhibition of pallidothalamic efferents; this in turn causes rapid changes and a loss of focused corticothalamic activity in cortical regions controlling cognitive and emotional processes. This results in rapid switching and an inability to filter inappropriate cognitive and emotional cortical information at the NAC level, manifested clinically as "flight of ideas" (rapid switching) and "loose associations" (unfiltered information) characteristic of psychosis.

Gray et al. (1991) have extended Swerdlow and Koob's (1987) model to include also a dorsal cortico-striato-pallido-thalamo-cortical circuit which is responsible for executing the steps of goal-directed motor programs. The function of the NAC system in this model is to monitor the smooth running of the motor program in terms of progress toward the intended goal and to switch between steps in the program, guided by the projections to the striatum from the prefrontal cortex, the amygdala, and the septohippocampal system. The latter is responsible for checking whether the actual outcome of a particular motor step matches the expected outcome, and this information is transmitted from the subiculum to the NAC. Positive symptoms of schizophrenia result

from a disruption in the subiculo-NAC projection that leads to a failure to integrate past regularities with ongoing motor programs. The role of DA in this model is identical to that described by Swerdlow and Koob, namely enabling switching of striatal activity into a new pattern by inhibiting striatal neurons and consequently disrupting lateral inhibition within the NAC. Gray et al. added a mechanism for a topographical specificity of DA effects, achieved by local DA increase in the region of active cortical (particularly subicular) glutamatergic terminals. Excess DA overcomes this topographical specificity, thus inhibiting striatal neurons indiscriminately, leading to a disruption of the running of all steps in all motor programs indiscriminately. Essentially the same process will be caused by loss of the subicular input to the NAC. Behavioral control will revert to new stimuli or familiar stimuli will be treated as novel. In psychological terms, this will be manifested in the weakening of the influence of past regularities on current behavior, and in a failure to monitor willed intentions correctly, which are considered by Gray et al. to be basic to the schizophrenic condition and to account for most of the positive symptoms of this disorder.

Both Swerdlow and Koob's and Gray and colleagues' models incorporate only mesolimbic DA hyperfunction and relatedly account only for positive symptoms of schizophrenia. In Swerdlow and Koob's model, negative symptoms were suggested to result from NAC cell loss, which would limit the amount of cortical information passing through the NAC, leading to paucity of affect and behavior. Swerdlow and Koob did describe the effects of DA underactivity in their limbic circuit and suggested that this would result in an inability to initiate or switch sets of cortical activity, leading to psychomotor retardation, paucity of affect, cognitive perseveration, and anhedonia, but this was proposed as a model of depression.

Carlsson (1988) proposed that striatal neurons can inhibit thalamocortical neurons and thus filter off part of the sensory input to the thalamus to protect the cortex from sensory overload and hyperarousal. Since DA inhibits (and glutamate excites) these striatal neurons, excess DA (or glutamatergic deficiency) should reduce this striatal protective influence and thus lead to psychosis. Recently, Carlsson et al. (1999, 2000) have updated the model by referring to the distinction between striatal neurons of the direct and indirect pathways. Specifically, they attributed the protective striatal function to neurons of the indirect pathway, and further suggested that neurons of the direct pathway exert an opposite, excitatory influence on thalamocortical neurons. Underactivity of the latter, induced for example by glutamatergic deficiency, is suggested to contribute to the negative symptoms of schizophrenia, whereas underactivity of the indirect pathway, induced by hyperactivity of DA or glutamatergic deficiency, is suggested to contribute to psychosis.

Csernansky et al. (1991) have also provided a model in which alterations in the limbic basal ganglia–thalamocortical circuit lead to the positive and negative symptoms of schizophrenia. According to their model, hippocampal activation of the circuit, by activating NAC neurons, results in inhibition of

behavioral output. DA can modulate this inhibition by inhibiting NAC neurons, thus inhibiting the circuit. In schizophrenia, abnormalities in limbic structures result in chronic increase in glutamatergic input to the NAC. Secondary to this increase, the level of NAC DA becomes reduced. Increased glutamatergic and decreased DA input to the NAC lead to overactivity of NAC neurons and thus overactivity of the circuit, and provide the pathophysiological basis of the prodromal/residual state of schizophrenia. The chronic decrease in DA in turn leads to an increase in the density of D_2 receptors in the NAC. As a result, an acute increase in NAC DA (e.g., by environmental stressors) will have an abnormally large disinhibitory effect on NAC neurons, leading to pathological release of behavior, i.e., to psychosis.

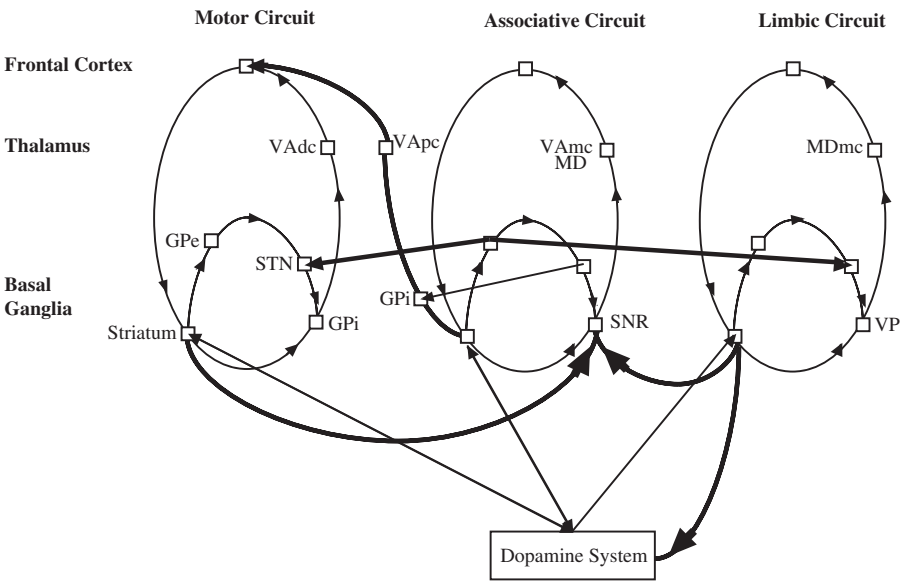
It should be noted that Swerdlow and Koob, Carlsson et al. and Csernansky et al. emphasize the loss of the inhibitory effects of the limbic circuit on behavior as the core abnormality of psychosis. In terms of current views of the organization of the basal ganglia–thalamocortical circuits, and as acknowledged by Carlsson et al. (1999, 2000), these three models can be reformulated as implicating underactivity of the indirect pathway in the pathophysiology of psychosis. The contribution of dysfunction of the indirect pathway to the florid state of schizophrenia is strengthened by the fact that in the early stages of Huntington's disease, which are characterized primarily by degeneration of striatal neurons of the indirect pathway, patients often show schizophrenia-like symptoms and are sometimes incorrectly diagnosed as suffering from schizophrenia (Joel and Weiner 1997; for an elaborated account see Joel 2001).

O'Donnel and Grace (1998) have recently described three different dysfunctional circuitries postulated to underlie the three clusters of schizophrenic symptoms as delineated by Liddle et al. (1992): reality distortion (positive), psychomotor poverty (negative), and disorganization. Positive symptoms are attributed to disrupted hippocampal and prefrontal inputs to the NAC shell, combined with an increase in phasic DA release and a decrease in prefrontal cortex-dependent tonic DA levels. These lead to a decrease in the overall cell activity in the NAC shell, resulting in abnormally depressed activity in the mediodorsal–prefrontal loop, leading to both hypofrontality and the emergence of positive symptoms, possibly via the orbitofrontal cortex. Psychomotor retardation is attributed to decreased input from the dorsolateral prefrontal cortex to the associative striatum, combined with the resultant decrease in tonic DA levels. These result in reduced activity of striatal neurons, leading to increased inhibition of the mediodorsal/ventroanterior–prefrontal loop, which is reflected in a perseverative state and an overall psychomotor retardation. The disorganization syndrome is attributed to disrupted input from the cingulate cortex and the ventrolateral prefrontal cortex, which lead to decreased activity of neurons of the NAC core. This will lead to increased inhibition of the reticular thalamic nucleus, resulting in a breakdown of thalamic filtering, as manifested in schizophrenics' inability to focus attention or maintain a coherent line of thought.

II. The Split Circuit Model of Schizophrenia

We have recently presented a new model of basal ganglia–thalamocortical organization, namely, the split circuit scheme, which emphasizes the open interconnected nature of the circuits (Joel and Weiner 1994, 1997, 2000), as opposed to the common view that these circuits are structurally and functionally segregated (e.g., Alexander et al. 1986, 1990; Alexander and Crutcher 1990). The model describes three open–interconnected split circuits, a motor, an associative, and a limbic, each containing a closed circuit through which information is channeled from a frontocortical subregion through specific subregions of the basal ganglia and thalamus back to the frontocortical area of origin, as well as several types of pathways connecting it to the other split circuits. The open–interconnected model is the first to explicitly incorporate the striatal connections with the dopaminergic system into a scheme of basal ganglia–thalamocortical circuits, in the form of closed and open loops (see Fig. 1 for a detailed description of the circuits and their interconnecting pathways).

In functional terms, we proposed that the motor, the associative, and the limbic split circuits provide the brain machinery for the selection and execution of goal-directed routine behavior, with the connections within each circuit subserving the selection of circuit-specific elements (motor acts, motor programs, and goals, respectively), and the connections between the circuits serving to coordinate their actions in order to produce complex goal-directed behavior (Joel and Weiner 1994, for a detailed exposition of the model see



Joel and Weiner 1999). In line with the widely held premise that the frontal cortex has a central role in flexible behavior, planning and decision making (e.g., Milner 1963; Luria 1973; Pribram 1973; Shallice 1982; Norman and Shallice 1986; Goldman-Rakic 1987; Fuster 1990; Kolb and Whishaw 1990; Robbins 1990, 1991; Levine et al. 1992; Stuss 1992), and the striatum subserves routine or automatic aspects of behavior (e.g., Cools 1980; Marsden 1982; Iversen 1984; Norman and Shallice 1986; Rolls and Williams 1987; Robbins 1990, 1991; Robbins and Brown 1990; Miller and Wickens 1991; Berridge and Whishaw 1992; Levine et al. 1992; Graybiel et al. 1994; Hikosaka 1994;

Fig. 1. A summary diagram of the structural organization of the motor, associative, and limbic split circuits. Each split circuit contains a closed circuit and an open route or an open pathway. The associative split circuit: The closed associative circuit comprises the associative striatum, SNR, VAmc, and MD thalamic nuclei and the associative prefrontal cortex (including the frontal eye field and dorsolateral prefrontal cortex). The open associative pathway arises from the associative striatum, traverses the associative GPi and VApc, and terminates in the premotor cortex, which projects to the motor striatum. The motor split circuit: The closed motor circuit comprises the motor striatum, motor GPi, VAdc, and the primary motor cortex and supplementary motor area. The open motor route consists of motor striatal projections to SNR. The limbic split circuit: The closed limbic circuit comprises the limbic striatum, ventral (limbic) pallidum, MDmc, and the limbic prefrontal cortex (including the orbitofrontal cortex and anterior cingulate area). The open limbic route consists of limbic striatal projections to SNR. There may also be an open limbic pathway arising from the limbic striatum and projecting via the rostromedial GPi to motor/premotor cortices. Included within each of the closed circuits as well as within the open associative pathway are a direct and a closed indirect pathway. In addition, the associative split circuit contains an open indirect pathway that connects it with the motor split circuit, and possibly an open indirect pathway that connects it with the limbic split circuit. Each split circuit has a closed loop with the DA system, and in addition, there are two open loops connecting the limbic split circuit with the motor and the associative split circuits. Abbreviations: *GPe*, external segment of the globus pallidus; *GPi*, internal segment of the globus pallidus; *MD*, mediodorsal thalamic nucleus; *MDmc*, mediodorsal thalamic nucleus, magnocellular subdivision; *STN*, subthalamic nucleus; *PFC*, prefrontal cortex; *VAdc*, ventral anterior thalamic nucleus, densocellular subdivision; *VAmc*, ventral anterior thalamic nucleus, magnocellular subdivision; *VApc*, ventral anterior thalamic nucleus, parvocellular subdivision. Definitions: Closed circuit: A striato-frontocortical pathway that reenters the frontocortical area which is the source of cortical input to this striatal subregion; Open pathway: A striato-frontocortical pathway that terminates in a frontocortical area which innervates a different striatal subregion; Open route: The striatonigral portion of an open pathway; Closed indirect pathway: An indirect pathway (striatum-GPe-STN-GPi/SNR) that connects functionally corresponding subregions of the basal ganglia, that is, which terminates in the same subregion of the basal ganglia output nuclei as the direct pathway; Open indirect pathway: An indirect pathway (striatum-GPe-STN-GPi/SNR) which connects functionally non-corresponding subregions of the basal ganglia, that is, which terminates in a different subregion of the basal ganglia output nuclei than the direct pathway; Closed loop: A loop (striatum-DA system-striatum) which terminates in the striatal subregion from which it originates; Open loop: A loop (striatum-DA system-striatum) which terminates in a different striatal subregion than that from which it originates. Pathways connecting between circuits are demarcated in *thick lines*

Marsden and Obeso 1994), within each circuit, the frontal component subserves a non-routine or non-automatic selection [similar to the supervisory attentional system in Norman and Shallice's (1986) scheme], whereas the striatal component acts as an automatic selection device [similar to the contention scheduling mechanism in Norman and Shallice's (1986) scheme; see Robbins 1990, 1991 and Wise et al. 1996].

Below we combine the split circuit scheme with the physiological and behavioral functions of DA as they have emerged from animal research, to present a detailed description of the circuits' contribution to normal goal-directed behavior and its modulation by DA. This model is then used to account for some symptoms of schizophrenia, based on the postulated dual DA dysfunction in this disorder as detailed by Grace and colleagues (Grace 1991, 1993, 2000; O'Donnel and Grace 1998; Moore et al. 1999). It is postulated that (1) routine goal-related information is actively maintained in the limbic striatum, and serves to direct and propel the selection and execution of motor plans by the associative and motor split circuits; (2) Striatal DA plays a fundamental role in the establishment, selection, and maintenance of routine goals as well as in limbic control of the associative and motor circuits because of its critical role in motivation, learning, and selection; and (3) The primary deficit of schizophrenia lies in an impairment of goal-directed control of routine behavior due to abnormal cortical and dopaminergic inputs to the limbic striatum. The latter is a revision and an elaboration of the idea that the cardinal deficit of schizophrenia lies in a failure to develop and maintain coherent patterns of goal-directed behavior (Bleuler 1911; Kraepelin 1919; Anscombe 1987; Frith 1987, 1992; Strauss 1987; Cohen and Servan-Schreiber 1992; Hemsley 1994; Liddle 1995; Zec 1995; Cohen et al. 1996, 1999; Friston 1998; Jahanshani and Frith 1998; Braver et al. 1999).

1. Striatum as a Contention Scheduling Device

Several characteristics of the striatum are important for understanding its functioning as a selection device. Striatal neurons are found in one of two stable subthreshold membrane potential states; a "down" state, in which the neuron is very hyperpolarized and does not generate action potentials, and an "up" state, in which the neuron is depolarized and a relatively weak excitatory synaptic input can trigger action potentials. The transition from the down to the up state depends on a temporally and spatially synchronized input from a relatively large subset of the neuron's cortical glutamatergic afferents (Pennartz et al. 1994; Houk 1995; Wilson 1995; Finch 1996; Gerfen and Wilson 1996; see Chap. 11, Vol. I). Given that the organization of corticostriatal projections is such that (1) different combinations of cortical inputs converge on different zones within a given striatal subregion and (2) each striatal neuron receives only few synapses from each of the thousands of cortical neurons innervating it (Flaherty and Graybiel 1993, 1994; Graybiel et al. 1994; Pennartz et al. 1994; Graybiel and Kimura 1995; Wickens and Kotter

1995; Wilson 1995; Finch 1996; Gerfen and Wilson 1996; Graybiel 1998), a striatal neuron's reaction to specific cortical inputs is likely to depend upon the current cortical context, i.e,. the pattern of activity in the different cortical regions which innervate this striatal neuron (Lidsky et al. 1985; Rolls and Williams 1987; Rolls and Johnstone 1992; Aosaki et al. 1994; Pennartz et al. 1994; Plenz and Aertsen 1994; Houk 1995; Houk and Wise 1995; Houk et al. 1995; Kimura 1995; Schultz et al. 1995a; Graybiel 1998). Moreover, these characteristics suggest that cortical context determines a set of possible striatal outputs corresponding to the set of striatal neurons that have been driven into the up state. The specific striatal output is determined by the firing induced in a subset of these neurons by specific cortical inputs, which together with a winner-take-all mechanism subserved by inhibitory axon collaterals or feed-forward inhibition by striatal interneurons (Groves 1983; Penney and Young 1983; Swerdlow and Koob 1987; Miller and Wickens 1991; Pennartz et al. 1994; Wickens and Kotter 1995; Wilson 1995; Kita 1996), restricts the number of activated neurons and serves to select one specific output.

An additional important characteristic of the striatal selection mechanism is its ability to be molded by experience, manifested in long-term changes in corticostriatal synaptic efficacy (Kimura 1987; Miller and Wickens 1991; Flaherty and Graybiel 1994; Pennartz et al. 1994; Schultz et al. 1995a; Wickens and Kotter 1995). Furthermore, it has been suggested that striatal neurons of the direct pathway "learn" to select the most appropriate element in response to specific stimuli, whereas neurons of the indirect pathway "learn" to suppress inappropriate elements (Houk and Wise 1995, Joel and Weiner 1999), as well as contribute to the termination of behavioral elements (Brotchie et al. 1991a,b; Obeso et al. 1994; Wichman et al. 1994a).

Under conditions requiring the selection of a new response strategy (e.g., during the initial stages of learning), the prefrontal cortex, interacting with different association and limbic regions, selects and directs behavior. Concurrently, the corticostriatal projections arising from these different cortical regions may drive a set of striatal neurons into the up state. Specific cortical activity patterns may then activate a subset of these neurons, of both the direct and indirect pathways, encoding the facilitation and suppression of specific behavioral elements, respectively. If the actual behavior leads to favorable outcomes to the organism, the activated corticostriatal synapses (both those responsible for the transition to the up state and those which induced firing) onto the activated striatal neurons of both pathways are strengthened, so that in the future this subset of neurons is more likely to be driven into the up state by the same or a similar cortical context and to be activated by the specific input.

Repeated occurrences of this sequence of events, i.e., reinforcement of a specific behavior in a specific context, will lead to the following: First, whenever the cortical context occurs it will drive a set of striatal neurons into the up state, thus determining a set of behaviors appropriate to that context as well as a set of behaviors inappropriate to that context. Second, the actual

behavior will be selected according to the specific cortical inputs to the neurons in the up state which will induce firing in a subgroup of direct pathway neurons, whereas inappropriate behaviors which may be triggered by these same cortical inputs will be suppressed due to the activation of indirect pathway neurons. Specific changes of the cortical input will activate other indirect and direct pathway neurons leading to the termination of the current behavior and to the initiation of a new behavior. Third, the behavior selected at any moment will be the most appropriate for the current situation according to past experience.

2. The Interaction Between the Striatum and the Frontal Cortex

Information regarding the selection of the most appropriate behavioral element in the current context is continuously channeled from the striatum to the frontal cortex via the basal ganglia output nuclei (SNR, internal segment of globus pallidus, ventral pallidum) and thalamus, and acts to bias the activity patterns of cortical neurons towards the selection of this behavior. Striatal information, however, does not necessarily translate into behavioral output since the frontal cortex receives in addition information about the current context from other cortical regions. Whether the actual behavioral output is the one selected by the striatum depends on the strength of the striatal biasing effect on the frontal cortex (which is a function of the degree of activation of striatal neurons), and on the degree of correspondence between the striatal and cortical biasing effects on the activity pattern in the frontal cortex.

In well-learned/highly familiar situations, striatal neurons which encode the most appropriate behavior, as well as those encoding incompatible behaviors, are expected to be strongly activated, and their strong biasing effect is expected to have a high degree of correspondence with the cortical biasing effect. The result is an effortless production of routine behavior. In novel or ill-learned situations, striatal neurons are expected to be weakly activated, and in addition, their (weaker) biasing effect on the activity of frontal neurons is unlikely to coincide with the biasing effects of other inputs to the frontal cortex. Under such circumstances the selection of behavioral output cannot be achieved automatically, but requires a supervisory process, subserved by the interaction of the frontal cortex with other brain regions (e.g., posterior association regions and high-order limbic cortices), which will yield alternative ways of action. In intermediate situations in which the cortical context is only partly familiar, striatal neurons will be activated, albeit less strongly than they would be in the fully familiar context, but their biasing effect is less likely to coincide with the cortical biasing effect. Two outcomes can ensue: (1) The cortical biasing effect may be sufficiently strong to counteract the striatal biasing effect; the routine behavior will not be performed, and the supervisory process will intervene. (2) The striatal biasing effect is sufficiently strong to lead to the execution of the routine behavior.

3. Contention Scheduling of Goals by the Limbic Striatum

The striato-frontal interaction described above takes place within each of the circuits, but on different types of information, namely, motor, cognitive, or limbic. Specifically, the motor striatum subserves the contention scheduling of simple motor acts, the associative striatum subserves the contention scheduling of motor programs (which include cognitive and motor components) and the limbic striatum subserves the contention scheduling of goals (Joel and Weiner 1999).

The proposition that the limbic striatum subserves the contention scheduling of goals, i.e., directs an organism's behavior toward specific end-points, e.g., obtaining appetitive stimuli (such as food, warmth, affection, the recognition of others), avoiding aversive stimuli (such as shock, anger, rejection), exploring novel stimuli, etc., is consistent with the current view, pioneered by Nauta et al. (1978) and Mogenson et al. (1980), that the limbic striatum plays a fundamental role in the translation of limbic information to action, that is, in the "directional" aspects of motivation (e.g., Robbins and Everitt 1982, 1992; Beninger 1983; Cador et al. 1989, 1991; Everitt et al. 1991; Scheel-Kruger and Willner 1991; Lavoie and Mizumori 1992; Schultz et al. 1992, 1995a; Kalivas et al. 1993; Pennartz et al. 1994; Salamone 1994; Beninger and Miller 1998; Depue and Collins 1999; Ikemoto and Panksepp 1999).

The proposition that goals are selected by a contention scheduling mechanism has the following implications: (1) Goals are selected according to their activation level which is determined by external and internal information (provided by the inputs to the limbic striatum); (2) As a result of a reinforcement-driven learning mechanism, the most appropriate goal is selected, that is, the goal that according to past experience is expected to maximize reward in the present situation; (3) In routine situations, the selection of goals is automatic and effortless; (4) In novel, ill-learned or dangerous situations, in which automatic selection of goals is not possible, a supervisory mechanism, residing in the limbic prefrontal cortex, selects a goal. These characteristics are in line with current views of goal-directed behavior according to which goals are activated by environmental and internal factors and selected in a way that maximizes expected value. In addition, it is accepted that when activity is well organized and routine, action moves from goal to goal fairly smoothly without requiring a deliberate "choice" or "decision" to change goals. The effortful process of selecting a goal is required under unusual internal or external stimulation (for review, see Pervin 1983, 1996).

4. The Role of Tonic and Phasic DA in the Contention Scheduling of Goals

What is needed for adaptive goal-directed behavior? The "goal system" must select (sometimes among several competing goals) the goal most appropriate to a given situation; maintain it throughout the course of the behavior; be resistant to interference; terminate it as soon as it is fulfilled or turns out to be

inadequate for the situation, and switch to a different goal. Current data and theories suggest that striatal DA is critically involved in these aspects of contention scheduling of goals.

While the physiological and behavioral consequences of striatal DA have been extensively documented (see Chap. 11, Vol. I; Chap. 19, this volume), they have been seldomly related specifically to the mode of DA release. However, it has been increasingly recognized that the two modes of DA transmission may play distinct roles in the modulation of corticostriatal synaptic transmission and plasticity, as well as in behavioral and cognitive processes (Grace 1991, 1993, 2000; Schultz 1998; Moore et al. 1999; Chap. 19, this volume).

a) Tonic and Phasic DA Release

DA cells exhibit two spontaneously occurring electrophysiological states: single spiking, in which the majority of cells are found, and burst firing (Bunney et al. 1991; White 1991; Kalivas 1993; Johnson et al. 1994; Grace 1995; Tepper et al. 1995). DA levels at the terminal fields depend on the firing mode of DA cells as well as on other factors acting directly on DA terminals. Specifically, there are two modes of DA release, phasic and tonic. The former refers to the release of DA during an action potential, which is rapidly inactivated via reuptake into presynaptic terminals and diffusion. The level of phasic release depends primarily on the mode of DA cell activity and is markedly enhanced when cells fire in bursts (Grace and Bunney 1984; Gonon 1988; Murase et al. 1992; Nissbrandt et al.1994; Garris et al. 1997). Tonic DA transmission represents the steady state DA level in the extracellular space. It is relatively constant and tightly regulated (Grace 1991, 1993). Tonic DA release may be driven by the presynaptic actions of glutamatergic cortical inputs onto DA terminals in the striatum, and is also affected by "spillover" from synaptic release (phasic) as well as by DA released from non-synaptic sites along the axons. As such, tonic DA would be secondarily affected by DA cell activity and directly affected by how much DA escapes from sites of release (e.g., via changes in release or reuptake; for a detailed description of phasic and tonic DA transmission, see Grace 1991, 1993, 2000; Moore et al. 1998).

Electrophysiological studies in behaving animals (Schultz 1986, 1998; Kiaytkin 1988; Schultz and Romo 1990; Miller et al. 1991; Schultz et al. 1992) have shown that DA cells switch to burst firing following the occurrence of salient, novel, or reinforcing (unconditioned and conditioned) stimuli. A critical feature of DA response is its dependence on event unpredictability: DA neurons respond to stimuli which have an innate or acquired (via learning) significance as long as they are unpredictable, but stop responding when they become predictable; during learning, DA responses transfer from primary rewards to reward-predicting stimuli. The responsiveness of striatal DA to significant stimuli has been supported also by in vivo microdialysis studies (Salamone et al. 1997; see Chap. 19, this volume).

Based on the above and the evidence for dopamine-dependent long-term changes in corticostriatal synaptic efficacy (Calabresi et al. 1992, 1996; Pennartz et al. 1993; Wickens et al. 1996; Charpier and Deniau 1997, see Chap. 11, Vol. I), it has been suggested that DA governs associative learning in the striatum by providing a "teaching" or an "error" signal which modulates corticostriatal synaptic transmission (Wickens 1990; Miller and Wickens 1991; Graybiel et al. 1994; Pennartz et al. 1994; Groves et al. 1995; Houk 1995; Houk et al. 1995; Kimura 1995; Pennartz 1995; Schultz et al. 1995a,b; Wickens and Kotter 1995; Graybiel 1998). The dependence of DA response on event unpredictability is also consistent with the theoretical positions and behavioral data that learning takes place only as long as the to-be-associated events are unpredictable (Rescorla and Wagner 1972; Pearce and Hall 1980).

While phasic DA plays a significant role in the processing of significant and unpredicted events, this cannot account for the wide range of behavioral deficits following injury to the DA system by means of lesions or pharmacological treatments (Schultz 1998). Overall, DA depletion or DA blockade result in a greatly impoverished behavioral repertoire and a disorganization of motivated, adaptive goal-directed interaction with the environment, ranging from locomotor activity, through species-specific behaviors like food hoarding and maternal nursing, to a wide variety of positively and negatively reinforced instrumental responding (Robbins and Everitt 1982; Beninger 1983; LeMoal and Simon 1991; Blackburn et al. 1992; Salamone 1994; Le Moal 1995; Beninger and Miller 1998; Di Chiara 1998; Schultz 1998; Ikemoto and Panksepp 1999). Importantly, many of the lost functions are still present but not expressed without DA, since they can be reinstated by DA agonists or strong environmental stimulation (Lynch and Carey 1987; Keefe et al. 1989; LeMoal and Simon 1991; Schultz 1998). These data have been interpreted as demonstrating that DA has a general enabling, activating, energizing, or invigorating function, attributed primarily to mesolimbic DA (Taylor and Robbins 1984, 1986; Cole and Robbins 1987; Le Moal and Simon 1991; Robbins and Everitt 1992, 1996; Salamone 1994; Salamone et al. 1997; Berridge and Robinson 1998; Di Chiara 1998; Schultz 1998; Ikemoto and Panksepp 1999; Chap. 19, this volume). Although gross manipulations of the DA system affect both phasic and tonic DA transmission, the observations that (1) DA alterations affect a wide range of behaviors, many of which do not trigger burst activity in DA cells; (2) DA agonists can reverse the effects of DA loss, although they do not restore DA phasic transmission (LeMoal and Simon 1991; Schultz 1998), and (3) artificial increases in DA level (e.g., by amphetamine) invigorate a wide range of behaviors (Lyon and Robbins 1975; Evenden and Robbins 1983; Taylor and Robbins 1984, 1986; Ljungberg and Enquist 1987), suggest that the enabling/energizing function of DA depends on tonic DA levels rather than on phasic DA release (Schultz 1998).

In view of the above, it has been suggested that the two modes of DA neurotransmission subserve different functions. Thus, Schultz (1998) concluded

that phasic DA subserves the signaling of significant alerting stimuli, and tonic DA subserves the enabling of a wide range of behaviors without temporal coding. Similarly, Moore et al. (1999) suggested that tonic DA provides sufficient level of DA receptor stimulation necessary for the initiation and execution of well-learned behavior, while phasic transmission is necessary for novelty-induced behaviors and learning. These authors (Grace 1991, 1993, 2000; Schultz 1998; Moore et al. 1999) have also described the modulation of corticostriatal synaptic transmission and plasticity by phasic and tonic DA which may mediate the functional role of DA in the striatum. Below we describe the role of striatal DA in contention scheduling with a focus on the contention scheduling of goals. DA is assumed to play the same role in the contention scheduling of motor programs and motor acts.

b) The Establishment of Goals in the Limbic Striatum

In the present model, the phasic increase in striatal DA following the unpredicted occurrence of conditioned and unconditioned reinforcers acts as a reinforcement signal which serves to strengthen synapses between active corticostriatal terminals and active striatal neurons. The strengthening of corticostriatal synapses on active direct pathway neurons will result in a greater likelihood that the encoded goal, which has led to favorable outcomes to the organism, is selected again in the same or a similar context. Similarly, the strengthening of corticostriatal synapses on active indirect pathway neurons will result in a greater likelihood that inappropriate goals are suppressed in the same or a similar context.

It should be noted that conditioned and unconditioned stimuli may act not only as reinforcers of the goal-directed behavior which precedes them, but also as stimuli guiding behavior. During learning, these stimuli acquire the capacity to activate direct pathway neurons encoding the next sub-goal as well as indirect pathway neurons encoding the previous sub-goal. Consequently, they will be able to trigger the termination of the previous sub-goal and the initiation of the next sub-goal, thus enabling a smooth transition between the different components of a routine goal-directed behavior. Thus, although these stimuli lose their ability to increase DA cell firing as they become predicted and therefore lose their ability to support further learning, they do not lose their ability to direct behavior.

c) Goal Selection

Striatal DA also serves to modulate the selection process (Schultz 1998; Moore et al. 1999). It has been suggested that by inhibiting striatal neurons or attenuating their responses to excitatory and inhibitory inputs (via activation of D_2 receptors; Uchimura et al. 1986; O'Donnel and Grace 1994; Cepeda et al. 1995; Yan et al. 1997, see Chap. 11, Vol. I), DA may restrict striatal output to the most strongly activated neurons (Yang and Mogenson 1984; Mogenson et al. 1993; Pennartz et al. 1994; Schultz et al. 1995; O'Donnel

and Grace 1998; Depue and Collins 1999; Moore et al. 1999). Furthermore, based on findings that activation of D_1 receptors enhances the response to excitatory glutamatergic input of striatal neurons in the up state but reduces the response of neurons in the down state (Kawaguchi et al. 1989; Cepeda et al. 1993, 1998; Hernandez-Lopez et al. 1997; Schultz 1998; Chap. 11, Vol. I), it has been suggested that DA increases the contrast gradient between weak and strong cortical inputs (O'Donnel and Grace 1998; Schultz 1998).

Since D_1 and D_2 receptors are expressed preferentially on striatal neurons of the direct and indirect pathways, respectively (Albin et al. 1989; Gerfen et al. 1990; Reiner and Anderson 1990; DeLong and Wichmann 1993; Gerfen and Wilson 1996), DA may simultaneously act (1) to suppress the activity of indirect pathway neurons, except for the most active ones, thus enabling the initiation (by direct pathway neurons) of a wide variety of goals while concomitantly preventing the selection of goals inappropriate to the current context, and (2) to enhance the contrast between neurons transferred to the up state by the cortical context and those which were not, thus ensuring that only context-appropriate goals will compete for behavioral expression. Since the selection process is modulated by the level of striatal DA, it is affected by both tonic and phasic DA release (see also section B.II.4.e below).

d) Goal Maintenance and Energizing

Once a goal is selected, tonic DA serves to maintain it at a sufficient level of activation and protect it from interference as well as to determine the effort which will be invested in attaining it. These functions are suggested to be subserved by the differential effects of activation of D_1 receptors on striatal neurons, depending on their membrane potential. Thus, tonic DA maintains the selected goal by facilitating firing of neurons already in the up state, and simultaneously provides protection from interference by suppressing firing or transition to the up state of neurons in the down state. Since most (about 80%) of D_1 receptors are in the low-affinity state (Richfield et al. 1989), these actions may be achieved either by activating the high-affinity D_1 receptors, or by local increases in DA level at the region of the active striatal cells which will suffice for activating low-affinity receptors. Such an increase may be achieved either via the stimulating effects of glutamate released from the active corticostriatal terminals on DA release (Grace 1991; Moore et al. 1999) or through the indirect facilitatory effects exerted by striatal neurons on DA cells (see below; see Kalivas et al. 1993 for a related view). The higher the levels of tonic DA, the higher the response of striatal cells to a given cortical input, and thus the higher is striatal facilitation of the selected output. In this way, the level of tonic DA determines the energy level of the selected goal.

An additional effect of the local increase in DA may be to activate D_2 autoreceptors. This activation may lead to reduced phasic DA release in response to DA cell firing. The consequences of such a decrease are detailed below.

e) Switching Between Goals

Based on lesion and drug studies showing that DA loss produces inflexible and perseverative behavior whereas increase in DA promotes behavioral switching, DA has been attributed a central role in switching (Lyons and Robbins 1975; Robbins and Everitt 1982; Oades 1985; Taghzouti et al. 1985; Swerdlow and Koob 1987; Van den Bos and Cools 1989; Weiner 1990; Gray et al. 1991; Le Moal and Simon 1991; Van den Bos et al. 1991; Pennartz et al. 1994). While the relationship between switching and tonic/phasic DA has not received attention, switching may be subserved by both modes of release depending on the conditions which elicit switching (Redgrave et al. 1999).

Goals are changed either in the course of routine chains of behaviors, namely, in response to predicted events, or when the situation unexpectedly changes, namely, in response to unpredicted events. Therefore, we suggest that the former depends on tonic DA whereas the latter depends on phasic changes in DA level. During routine behavior, the attainment of each sub-goal of a routine motor program is predicted, and thus not accompanied by phasic changes in striatal DA. Rather, switching between goals during the performance of routine goal-directed behaviors is subserved by the mechanisms detailed above for goal selection, namely, the attainment of a sub-goal triggers both its termination and the initiation of the subsequent sub-goal by activating neurons of the indirect and direct pathways, respectively. In this way, tonic DA enables smooth transition between successive sub-goals.

The phasic increase in striatal DA accompanying the unexpected occurrence of significant events depresses the activity of indirect pathway neurons, retarding the suppression of all goals, except for the inappropriate ones (see section B.II.4.c), thus reducing constraints on the concomitant goal selection by direct pathway neurons. The DA effects on direct pathway neurons are more selective. Specifically, via its differential action on neurons that are in the up vs down state, DA facilitates the selection of a context-appropriate goal. Moreover, it biases the selection away from the goal that had been active just before the unexpected occurrence of a significant event. This is achieved by the attenuation of the phasic DA increase in the region of striatal neurons that have just been active, as a result of activation of DA autoreceptors in this region (see section B.II.4.d). Such attenuation may serve to favor the selection of new sets of neurons, i.e., of new goals, as well as to prevent switching back to the set which has just been active, thereby preventing dithering between goals (Redgrave et al. 1999).

It should be pointed out that phasic increase in striatal DA is hypothesized to mediate both switching and learning. Thus, increased DA input to the striatum following unexpected significant stimuli, both facilitates a switch in the set of active striatal neurons from the set which has just been active to a new set, thus favoring a change in behavior, and strengthens active corticostriatal synapses of neurons which have just been active, thus raising the like-

lihood that these neurons will be activated again by this cortical context, and thus that the behavior will occur again in the same or a similar situation.

Finally, phasic changes in striatal DA may also contribute to the termination of a goal-directed behavior which has proved to be ineffective. DA neurons were found to decrease their firing rate in response to the omission of an expected stimulus (Schultz et al. 1993, 1995b). This may lead to a transient decrease in tonic DA levels, which will affect particularly high affinity D_2 receptors (Schultz 1998). The decreased activation of these receptors may lead to increased activity of neurons of the indirect pathway, including those which encode the termination of the current goal, thus leading to a behavioral arrest which enables a reevaluation of the situation and a reselection of a goal.

5. The Translation of Goals to Behavior

In the present scheme, the limbic split circuit selects goals, without specifying the specific motor program by means of which these goals are to be achieved. The latter is suggested to be the function of the associative split circuit acting together with the motor split circuit. However, via its connections with these circuits, the limbic split circuit directs the selection and execution of motor programs towards achieving the selected goal.

Specifically, information regarding the most appropriate goal in the current context:

1. Is channeled from the limbic striatum via the open limbic route to SNR, where it acts to bias nigral output according to the current goal of the organism. In this way selection of goals in the limbic striatum can affect the transfer of information in the striato-nigro-thalamo-cortical pathway to the associative prefrontal cortex, which is involved in the selection and execution of motor programs. It can also affect the nigral output to the superior colliculus and in this way contribute to the reallocation of attention when the goal is changed or when a novel or surprising stimulus appears.
2. Modulates the dopaminergic input to the limbic striatum as well as to the motor and associative striatum, via the closed and open loops originating from the limbic striatum. We have recently suggested that via each of the loops, closed or open, the striatum exerts a direct inhibitory effect on DA cells as well as an indirect disinhibitory effect, i.e., facilitation of burst firing in DA cells (Joel and Weiner 2000). Thus, the activation of a set of limbic striatal neurons encoding a specific goal is expected to directly inhibit dopaminergic neurons. This inhibition can counteract the excitatory input to the dopaminergic cells when the goal is attained and thus prevent the firing of dopaminergic neurons to predicted rewards (Schultz et al. 1993, 1995b; Wickens and Kotter 1995; Brown et al. 1999). In this way, the limbic striatum can prevent switching following the attainment of sub-goals in the course of performing a routine goal-directed behavior, as well as restrict learning in all striatal subregions in well-learned situations. The indirect

facilitatory effect of the limbic striatum on DA cells stems from the projections of striatal neurons onto GABAergic neurons in SNR and VTA and their subsequent projections onto DA cells as well as onto the GABAergic neurons of the limbic pallidum, which also project onto DA cells. These disinhibitory effects may provide a mechanism whereby the limbic striatum can adjust DA levels in the different striatal subregions according to the motivational state of the organism, and thus modulate the degree of effort invested in the execution of the encoded goal-directed behavior (Joel and Weiner 2000; for a related view see Kalivas et al. 1993).

3. Is continuously channeled to the limbic prefrontal cortex where it acts to bias the activity patterns of cortical neurons towards the selection of this goal and contributes to sustained activity of limbic prefrontal cortex neurons, which maintain active goals and intentions in the absence of the external and internal stimuli that arouse them. From the limbic prefrontal cortex the information can be channeled to the associative split circuit via corticocortical connections between the limbic prefrontal cortex and the associative prefrontal cortex. The projections from the limbic prefrontal cortex to the associative prefrontal cortex may directly bias the selection of motor programs by the associative prefrontal cortex according to the current goal, encoded in the limbic prefrontal cortex. As both prefrontal regions subserve a supervisory mechanism, this link may be particularly important for the effortful and deliberate process of goal selection. This is in contrast with the transfer of information via the different open pathways that subserve an automatic, effortless process by which goals can affect different aspects of behavior.

6. Schizophrenia

A failure to exert control over thoughts and actions has been often considered to be central to schizophrenia (Kraepelin 1919; Anscombe 1987; Frith 1987, 1992; Strauss 1987; Cohen and Servan-Schreiber 1992; Hemsley 1994; Liddle 1995; Zec 1995; Cohen et al. 1996, 1999; Friston 1998; Jahanshani and Frith 1998; Braver et al. 1999). Given that a core characteristic of coherent and flexible behavior is that it is goal-directed or purposeful, the failure of control in schizophrenia has been attributed to a disruption of a system which allows the generation of efficient goal-directed behaviors. Influenced by Kraepelin's (1919) view that schizophrenia is a disorder of volition, Shallice and Norman's (1986) supervisory attentional system and Frith's (1987, 1992) powerful exposition of schizophrenia as a disorder caused by a breakdown in the monitoring of willed intentions, there has been an increasing trend to argue that schizophrenic symptomatology may reflect a failure of high-level cognitive control system or of a central executive mechanism which guides and coordinates behavior in a flexible fashion, particularly in novel and complex situations. Such control has been typically envisaged as a top–down process, with the level of control being "higher" to lower level selection (Redgrave

et al. 1999), and most typically residing in the prefrontal cortex (Kraepelin 1919; Frith 1987, 1992; Strauss 1987; Weinberger et al. 1988; Robbins 1990, 1991; Cohen and Servan-Schreiber 1992; Liddle 1995; Weinberger and Lipska 1995; Zec 1995; Cohen et al. 1996, 1999; Crider 1997; Jahanshani and Frith 1998; Braver et al. 1999).

We would like to forward a different view: Most of human behavior, whether internally or externally driven, is routine, and most of the time people do not face novel and complex situations. Indeed, what makes the normal adult behavior smooth, flexible, and adaptive is that most of the time people transact with fairly familiar internal and external environments, which elicit routine goal states that give rise to routine behavioral programs. Moreover, when the "executive" comes into play, its role in most cases is to stop the ongoing inappropriate routine behavior and aid in choosing an alternative behavior from the existing repertoire; it is only in very unfamiliar and unexpected situations that a dramatic re-appraisal and re-learning are needed. Finally, when normal persons face unfamiliar and unexpected situations for which they do not have a routine behavioral program or one that is easily adaptable to the situation, they do not fair out very well either.

While we accept the position that schizophrenia involves a disturbance in executive functions, the pervasiveness of the schizophrenic deficits in almost all aspects of functioning points in our opinion to a profound disturbance also in the routine aspects of behavior. Indeed, in these patients "problems may be noted in any form of goal-directed behavior leading to difficulties in performing activities of daily living such as organizing meals or maintaining hygiene" (DSM-IV, p 276). We propose that precisely such a disturbance of routine goal-directed behavior results from a disruption of the contention scheduling of goals in the limbic striatum due to cortical dysfunction and a dysregulation of phasic and tonic DA, and the resultant dysfunction of the limbic, associative, and motor split circuits. On this view, schizophrenic symptomatology, rather than reflecting a failure of top-down control, reflects an impaired interplay between top-down and bottom-up control processes within each circuit, as well as impaired "medial-to-lateral" control processes between the circuits.

We want to note that our account of DA dysfunction is limited to the striatal portion of the circuits and does not include the well-documented DA role in the frontal component of the circuit, e.g., in working memory and many other executive functions (Chap. 19, this volume). Likewise, while our model retains the notion of an "impaired executive" or deficient supervisory processes in schizophrenia, it is silent with regard to the direct contribution of prefrontal and temporal dysfunction to schizophrenic symptomatology, which has been described in detail by others (e.g., Weinberger 1987, 1988; Cohen and Servan-Schreiber 1992; Cohen et al. 1996, 1999; Goldman-Rakic 1999; Chap. 19, this volume). This is because the dysfunction of these regions is considered to disrupt supervisory processes which are important in novel or non-routine situations, whereas our model focuses on routine behavior and therefore on the basal ganglia.

Finally, we adhere to the notion that schizophrenia is a neurodevelopmental disorder (e.g., Murray and Lewis 1987; Bogerts 1991, 1993; Mednick et al. 1991; Murray et al. 1991; Harrison 1995, 1999; Knable and Weinberger 1995; Weinberger and Lipska 1995; Turner et al. 1997; Weickert and Weinberger 1998; Keshavan 1999; Keshavan and Hogarty 1999), in which an early damage (occurring in utero or in early neonatal period) to prefrontal and/or temporolimbic cortices interacts with the development of the brain to lead via as yet unknown (but widely speculated; e.g. Knable and Weinberger 1995; Weinberger and Lipska 1995; Friston 1998; Keshavan 1999; Keshavan and Hogarty 1999) mechanisms to the late appearance of symptoms.

a) Fronto-temporo-limbic Cortical Dysfunction and Dysregulation of Tonic and Phasic DA Transmission in Schizophrenia

As noted in the introduction, based on extensive evidence of morphometric abnormalities in frontal and temporal cortices, and on neuroimaging studies of brain function in patients with schizophrenia pointing to an abnormal pattern of fronto-temporal activation/interaction, it has been increasingly accepted that schizophrenia involves an abnormality in prefrontal-temporal neuronal and/or functional connectivity (Liddle 1987, 1995; Friston et al. 1992; Weinberger et al. 1992; Friston and Frith 1995; Frith et al. 1995; Garey et al. 1995; Glantz and Lewis 1995; Knable and Weinberger 1995; Spence et al. 1997; Selemon et al. 1995, 1998; Fletcher et al. 1996; Dolan and Fletcher 1997; Jahanshani and Frith 1998; Rajkowska et al. 1998; Goldman Rakic 1999), and that this abnormality leads to a dysregulation of mesolimbic DA.

Grace (1991, 2000; O'Donnel and Grace 1998; Moore et al. 1999) has advanced a refined hypothesis of mesolimbic DA dysfunction based on the dual control of DA release in the NAC. In this model, tonic DA levels regulate phasic DA release via activation of DA synthesis- and release-modulating autoreceptors, so that the amount of phasically released DA is an inverse function of the basal level of tonic DA present in the extrasynaptic space. A pathological decrease in the activity of cortical inputs to the NAC leads to a reduction in tonic DA release, leading to a decrease in the basal extracellular levels of DA in the NAC. The resultant decrease of DA terminal autoreceptor stimulation leads to abnormal enhancement of spike-dependent DA release. Consequently, cell firing, and in particular, bursting of DA cells would lead to a release of abnormally large amounts of DA, and produce pathologically high degrees of postsynaptic receptor stimulation (for a detailed description see Grace 1991, 1993, 2000; O'Donnel and Grace 1998; Moore et al. 1999).

b) The Consequences of Fronto-temporo-limbic Cortical Dysfunction: Disrupted Establishment of Goals

The abnormal functioning of fronto-temporo-limbic cortical regions and the resulting disorganized fronto-temporo-limbic input to the limbic striatum is expected to lead to an abnormal establishment of goals in the limbic striatum.

As a consequence of disrupted functioning of and information flow between fronto-temporo-limbic cortical regions, the effortful goal selection process in non-routine situations that takes place in the limbic prefrontal cortex in concert with temporo-limbic regions will be abnormal. Goal selection will be less determined by information in temporo-limbic regions, e.g., about one's own emotions and those of others, the significance of stimuli and events, and memories/knowledge related to the current situation, so that many of the selected goals will be unrelated or inappropriate to the context. Since reinforcement of most behaviors is context dependent, i.e., the same behavior is reinforced in some situations but not in others, many of the individual's behaviors will be inconsistently reinforced or punished.

Since the establishment of goals in the limbic striatum progresses concurrently with goal selection in the limbic prefrontal cortex, and depends on repeated reinforcement of the selected goal, it will also be abnormal. Specifically, the striatum will learn to select only those goals which are reinforced or at least not punished under most situations familiar to the individual, leading to the establishment of a limited repertoire of goals, mostly avoidant in nature. Moreover, goals established in the striatum will be less context-dependent than normal, i.e. their activation will be more dependent on specific information derived mostly from the limbic prefrontal cortex, and less dependent on the cortical context derived from temporo-limbic regions.

It is, therefore, hypothesized that many of the persisting deficit symptoms in schizophrenia result from the individual's inability to acquire through life experiences a rich repertoire of goals which can be automatically selected in a context-appropriate fashion and lead to behaviors which are appropriate and thus reinforced. This will lead in general to poverty of behavior as well as to inappropriate behavior and withdrawal. In addition, since interpersonal interaction and communication are probably the most context-sensitive human behaviors, often requiring complex processes of inferring the right context (see Sperber and Wilson 1987), they are likely to be most adversely affected by a dysfunction in the mechanism responsible for the selection of context-appropriate goals. This may account for the pervasive impairment of schizophrenic individuals in the social domain, characterized by poor social relations and social skills, lack of interpersonal competence, and lack of the ability to engage in socially appropriate behaviors (Dworkin 1992).

The dysfunctional process described above presumably takes place throughout the life of an individual destined to become schizophrenic, consistent with the observation that some dysfunction may appear already in the prodromal stage. Such dysfunction is mainly characterized by negative symptoms, such as social withdrawal and isolation, although they are much milder than they are after the schizophrenic illness begins (Davis et al. 1991; Faustman and Hoff 1995). The variability of presenting symptoms in the prodromal stage is likely to reflect differences in the severity of cortical abnormalities and in the life experiences of each individual. This is in line with the observation that individuals with more evidence of structural brain abnormalities have a poorer premorbid adjustment, more prominent

negative signs, symptoms, and cognitive impairments, and a poorer outcome (DSM-IV).

It should also be pointed out that the above account does not incorporate a DA dysfunction, since it is not clear whether such a dysfunction is expressed prior to the first psychotic episode. However, in some cases it may be present already at the prodromal stage, as evidenced by the presence of mild positive-like symptoms (e.g., odd beliefs but not of delusional proportion; DSM-IV).

c) The Consequences of Dysregulation of the DA Input to the Limbic Striatum

α) Reduced Tonic DA: Goal Selection, Activation and Maintenance

In familiar, routine situations, tonic DA provides a sufficient level of DA receptor activation, permitting the selection and maintenance of goals. A reduction of tonic DA release and of tonic DA levels in the limbic striatum of schizophrenic patients will thus lead to deficits in goal selection, maintenance, and energizing. Specifically, a reduced DA level will lead to insufficient activation of neurons of the direct pathway, and thus to difficulties in the initiation of goals. This will be compounded by an insufficient inhibition of neurons of the indirect pathway and thus an overinhibition of all goals, which will further impair the initiation (by direct pathway neurons) of the most appropriate goal. In addition to difficulties in the selection of an appropriate goal, the loss of DA-energizing effect will result in a weak activation of the selected goal. Low motivation, apathy, loss of interest or pleasure (anhedonia), restriction of the range and intensity of emotional expression and reactivity (flat or blunted affect) will follow.

Sufficient DA levels are needed not only for "energizing" the selected goal, but also for preventing the activation of competing goals. Therefore, weak activation of the selected goal may lead to difficulties in maintaining the selected goal in the face of relatively minor changes in the situation, i.e., to increased sensitivity to interference. It should be noted that since such minor changes are by definition not accompanied by a rise in DA level, the newly selected (interfering) goal is also of low energy. Therefore, the patient is expected to switch repeatedly between different low-energy goals. Reduced goal activation may also result in a gradual decay of goal representation, which may eventually result in the cessation of goal representation in the limbic striatum.

Weak activity of striatal neurons of the direct pathway will result in a weak biasing effect on the activity of the limbic prefrontal cortex. This will disrupt the automatic selection and maintenance of goals in the limbic prefrontal cortex in routine situations, thus requiring a supervisory mechanism for the selection of goals, as normally happens in ill-learned situations. Moreover, since the supervisory process depends on interactions of the limbic prefrontal cortex with other association and limbic cortical regions, and these inter-

actions are dysfunctional in schizophrenia, the goal selection process will not only cease to be automatic and effortless but will also be impaired (as described in the previous section).

The dysfunction of the limbic striatum as a consequence of reduced tonic DA will not only affect the functioning of the closed limbic circuit, as described above, but also its modulation of the functioning of the motor and associative circuits, enacted via the open limbic route and the open loops. Thus, reduced goal activation in the limbic striatum may lead, via reduced activity of the open loops, to a reduction in the facilitating, i.e., disinhibiting, effects of the active limbic striatal neurons encoding a goal on tonic DA levels in the associative and motor split circuits. As a consequence, the degree of effort invested in performing the relevant goal-directed behavior, which depends on tonic DA levels in the motor and associative split circuits, will be lowered. Reduced DA input to these circuits will also lead to difficulties in initiating goal-directed activities (avolition), manifested in decreased behavioral output and reduction in the production of thought and speech (alogia).

Reduced goal activation will also lead to a reduction in the inhibitory effect of the active limbic striatal neurons encoding a goal on the phasic response of DA neurons to the occurrence of this goal, and thus to an abnormally high phasic response of DA neurons. The consequences of the resultant abnormal phasic DA release in the three striatal regions are detailed in the next section. In addition, such an abnormal phasic response of DA cells may disrupt the functioning of the closed associative circuit by interfering with the throughput of associative striatal information via SNR. We (Joel and Weiner 2000) have recently suggested that striatal input to SNR leads to local increases in dendritically released DA in the regions of SNR neurons that were inhibited by the striatal input. This local DA increase acts to increase signal to noise ratio in striatonigral transmission because it (1) increases (via D_1 presynaptic receptors) GABA release from the active striatal terminals in the regions of inhibited SNR cells but not in other SNR regions innervated by the active striatal neurons, and (2) excites (via D_2 postsynaptic receptors) SNR neurons in the vicinity of the inhibited SNR cells, thus increasing the contrast between the inhibited SNR cells which transmit striatal information and other SNR cells. Since one of the factors increasing dendritic release is the switch of DA cells from the single spiking mode to the bursting mode, loss of the regulation of DA neurons burst firing by the limbic striatum will lead to an unregulated dendritic release and thus loss of the spatially restricted increase in dendritic release. Consequently, the sharpening of striatal neurotransmission will be lost, disrupting associative striatal throughput via SNR to the associative prefrontal cortex and the superior colliculus, thus impairing the selection and execution of motor plans as well as the allocation of attention.

Loss of an active goal representation in the limbic striatum may also lead, via reduced activity of the open limbic route, to a disintegration of the modulating effect of the limbic striatum on the selection and execution of motor programs in the associative split circuit. As a consequence, behavior

will be triggered by any event which can activate motor programs in the associative striatum, including stimuli or thoughts that have established strong stimulus-response associations in the associative striatum as well as motor or cognitive components of well-learned motor programs. Behavior will be either stimulus-bound or disorganized, as each of the executed elements may lead to the next element in the same motor program or to elements of other motor programs. These would be reflected in a wide range of stereotypic behaviors, ranging from simple motor acts such as pacing and rocking, to more complex ritualistic behaviors documented in schizophrenic patients; disorganized speech or loosening of associations, i.e., slipping off the track from one topic to another; as well as disorganization of any form of goal-directed behavior.

It should be pointed out that at the behavioral level, it would be difficult to distinguish between abnormal behavior which results from repeated switching between low-energy goals and that resulting from reduced modulation of behavior by goals, because both would be reflected in a failure to persist in goal-directed behaviors. We presume, however, that the two deficits would be accompanied by different subjective experience. Thus, premature switching of goals should still allow subjective perception that behavior is related to one's goals, whereas a dissociation between goals and behavior may lead to feelings of loss of control, and even to a feeling of alienation towards one's behavior.

β) Abnormal Phasic DA Release: Learning and Switching

Normally, phasic DA, occurring following the encounter of unexpected significant events (external or internal), facilitates the acquisition of new goals as well as switching between already established goals. The dysregulation of phasic DA will lead to exaggerated phasic DA release in response to stimuli which normally lead to phasic DA release, such as novel or unexpected reinforcing stimuli (exaggerated phasic release), as well as to phasic DA release in response to stimuli which normally would not lead to such release, such as weak novel stimuli, repeatedly presented stimuli, and predictable reinforcing stimuli (inappropriate phasic release).

Since phasic increase of striatal DA facilitates switching between goals, increased phasic DA release will lead to switching following the occurrence of events which are not relevant to the current goal and which normally would not have led to phasic DA release, as well as following the expected occurrence of goal-related events (i.e., achieving a sub-goal), which although expected will lead to phasic DA release. Both will lead to repeated premature abortion of current goals and re-selection of different goals, leading to high distractibility. Importantly, the patient may be distracted not only by task-irrelevant stimuli, as is widely documented, but also following the completion of each step of the goal-directed behavioral sequence. This should lead to profound difficulties in persisting in any goal-directed behavior. Moreover, since DA inhibits neurons of the indirect pathway, increased phasic DA release may lead to abnormal suppression of indirect pathway neurons, including those

encoding the suppression of inappropriate goals. Thus, the patient will not only be highly distractible, but will also be more likely to switch to inappropriate goals, leading to inappropriate or bizarre behaviors.

In addition to disrupting goal-directed behavior, increased phasic DA release may charge events with a particular intensity and give rise to spurious sense of significance (Anscombe 1987) at the experiential level; moreover, phasic DA release in response to task-irrelevant and task-relevant events will give rise to different subjective interpretations/experience. The former will lead to the attribution of heightened significance to insignificant stimuli, resulting in the widely documented attraction of schizophrenics to irrelevant stimuli (Kraepelin 1919; Zec 1995), whereas the latter will lead to attribution of heightened significance to one's own actions. Thus, whereas normally the attainment of an expected goal as a result of performing the routine goal-directed behavior is not accompanied by changes in striatal DA levels and thus remains "unnoticed," abnormal phasic DA increase following the attainment of a goal after performing the relevant goal-directed behavior, may lead to inappropriate feelings of achievement, excitement or surprise, or an excessive sense of personal agency in schizophrenic patients. This may contribute to grandiosity delusions. A similar misattribution of significance/achievement to other people's routine actions may contribute to suspiciousness, hostility, and paranoid delusions.

The difficulties in performing goal-directed behaviors resulting from inappropriate switching between goals in the limbic striatum may be compounded by the consequences of exaggerated and inappropriate phasic DA release in the associative and motor striatum, namely, over-switching between motor programs and between components of motor programs. The over-responsiveness of the DA system may also lead to excessive triggering of motor programs by current stimuli and thoughts so that motor programs will be under less control by goals selected in the limbic striatum (normally exerted via the open limbic route). This may lead to a gross disorganization in the performance of activities of daily living such as organizing meals or maintaining hygiene as well as disorganized speech or loosening of associations. At the experiential level, dissociation between goals and behavior will lead to feelings of loss of control and alienation towards one's behavior. In the extreme case, delusions of alien control, i.e., attribution of one's actions to an external agent, may appear.

During psychotic episodes, increased phasic DA release is likely to lead to periods of increased tonic DA (Moore et al. 1999). Under these conditions selected goals will be over-activated, leading to a disproportional effort in attaining them. In addition, since DA has a focusing effect, increased tonic DA will lead to a reduction in the number of alternative goals which are activated enough to be selected, leading to reduced variability of behavioral output (Lyon and Robbins 1975), so that the patient will alternate between relatively few behaviors, each executed with great effort. Since the degree of activation depends on the degree a specific goal has been learned in the current context,

only well-learned goals will be activated enough to be selected. Moreover, since DA acting on D_1 receptors facilitates the activity of already active neurons, and since the normal mechanism by which already active goals have less chances of being reselected, is likely to be overwhelmed by the high DA level, the current goal will be not only highly activated but also hard to replace. These may be further exaggerated by DA inhibitory effects on neurons of the indirect pathway that are responsible for suppressing or terminating the current goal as well as for suppressing inappropriate goals. Therefore, prolonged periods of increased phasic DA may lead to highly motivated, inappropriate, stereotypic, and perseverative behavior.

Increased tonic DA levels may result in an additional problem. Since striatal neurons of the direct pathway are highly active, their biasing effect on the limbic prefrontal cortex is expected to be abnormally high. Under such conditions, the biasing effect exerted on the limbic prefrontal cortex by other cortical regions might not be sufficient to counteract the strong striatal biasing effect, resulting in great difficulties in resisting the performance of routine goal-directed behavior. This may be reflected in a high rate of "capture errors," i.e., performing the routine behavior instead of a behavior one intended to, and may be experienced as being forcefully driven to perform specific behaviors in spite of intentions to behave differently. At the extreme the patient may feel as if he has no free will, or as if his free will has been overtaken by some strong and alien force.

In addition to facilitating switching, phasic increase in striatal DA levels governs striatal learning. Therefore, increased phasic DA release will lead to a rapid learning of new goals, motor programs, and motor acts, as well as to over-learning of routine goals, motor programs, and motor acts in the limbic, associative, and motor circuits, respectively. Moreover, the inappropriate phasic DA release to incidental/insignificant stimuli and to predicted reinforcers will lead to inappropriate learning, i.e., to the establishment of goals with odd or bizarre content, and to the acquisition of superstitious behaviors that are performed as a part of a goal-directed sequence, although they are not necessary for attaining the goal. During a psychotic episode, this will be reflected in the development of highly energized bizarre behaviors that gradually replace previous behaviors. At the experiential level, abnormally rapid and redundant associations, seeing relationships where they do not exist, and excessive perception of a correspondence between one's goals and chance occurrences of external events, may lead to magical thinking, ideas of references, exaggerated inferential thinking (delusions), and the breaking of boundaries between the inner and the outer worlds.

Even more critically, the faulty learning occurring during each psychotic episode will increasingly broaden the patient's repertoire of inadequate and bizarre goals and behaviors. This may account for the findings that considerable proportion of patients experience some progression of their illness, with recurrent psychotic episodes resulting in lower levels of recovery and higher levels of residual symptoms, and that the longer the period of psychosis expe-

rienced prior to receiving APD treatment, the poorer the treatment response and the outcome (Huber et al. 1980; May et al. 1981; Wyatt 1991; Loebel et al. 1992; McGlashan and Fenton 1993; Lieberman et al. 1996, 1997; McGlashan 1999). Likewise, cumulative defective learning experience is consistent with findings that assertive rehabilitation efforts appear to improve long-term outcome (Davidson and McGlashan 1997).

d) Summary: Phasic and Tonic DA Dysregulation and Schizophrenia Symptoms

As may be evident from the discussion thus far, both abnormally low tonic DA and high phasic DA are hypothesized to lead to similar deficits, including excessive and immature switching, perseveration, disorganization, and a dissociation between goals and behavior. The two states are suggested to differ in what may be termed the "energy level" accompanying the observed deficit: low energy with low tonic DA and high energy with increased phasic DA. It is precisely such a difference in energy level that seems to distinguish productive from deficit symptoms, and indeed may be discerned in the symptom description of DSM-IV. Thus, positive symptoms are said to include "grossly disorganized behavior: problems may be noted in any form of goal-directed behavior leading to difficulties in performing activities of daily living such as organizing meals or maintaining hygiene," whereas under negative symptoms, the description appears as "Avolition: is characterized by inability to initiate and persist in goal-directed activities. The person may sit for long periods of time and show little interest in participating in work or social activities." Likewise, positive symptoms include "Catatonic motor behaviors . . . which range from extreme degree of catatonic stupor to purposeless and unstimulated excessive motor activity," while negative symptoms include "Abnormal psychomotor activity, e.g., pacing, rocking or apathetic immobility, odd mannerisms, posturing, ritualistic or stereotyped behavior"; and positive symptoms include "loosening of associations, disorganized speech," while negative symptoms include "problems with focusing attention, distractibility." In general, boundary problems in classification and diagnosis of schizophrenia symptoms are widely acknowledged (Strauss et al. 1974; Frith 1987; Andreasen 1982; Bilder et al. 1985; Cornblatt et al. 1985; Frith 1987; Carpenter et al. 1988; Carpenter and Buchanan 1989; Kay 1990; Lyon 1991; Robbins 1991; Tandon and Greden 1991; Andreasen et al. 1995; Tandon 1995; Crider 1997). As pointed out by Lyon (1991), one of the reasons for such problems may stem from an excessive focus on the "content" of the aberrant behaviors rather than on its "structure"; Indeed, our account resonates with that of Lyon (1991) who suggested that schizophrenia symptoms may be grouped under four major types of behavioral change: switching, focusing, fragmentation, and stereotypy.

Differences in "energy level" will be reflected in the accompanying subjective (and therefore communicated) experience. In the low energy state,

the patient will primarily feel unenergetic, unable to carry out his intentions and plans, passive, apathetic, withdrawn, and displaced. In the high energy state, the patient may feel highly energetic, overwhelmed with a sense of personal significance, meaning and control, or controlled by great powers, culminating in delusions. As summarized by Anscombe (1987), "some patients describe an animated world full of significance while others describe experience that is empty and null" (p. 242).

Energy level may also be reflected in the severity of the symptoms. In particular, in low energy the processes involved are relatively slow and weak, enabling the supervisory systems to correct at least some of the deviance; in high energy, the supervisory systems, which are by themselves malfunctional, collapse, which will be reflected in a more extreme behavioral disorganization.

The most devastating consequence of either abnormally low or abnormally high DA in the limbic striatum is the splitting between goals and behavior. In both cases, the patients become disconnected from the motivational and intentional origins of their behavior, cannot give coherence to their behavior, loose sense of control, and increasingly become observers of their behavior rather than its initiators. Moreover, it is the "routineness" of one's goals and actions, i.e., the rapid and efficient choice of well-known courses of action in different situations, and the correspondence between purpose and outcomes which render one's behavior coherent to oneself and to others and link the person's inner world with the objective outer world. One can say that I know myself because I am familiar with the actions I take in different situations. In addition, since most adult individuals belonging to the same class, culture, etc., share many routine goals and actions, this ensures social coherence and approval. Repeated activation of goals and actions that lack routineness and coherence and are situation-inadequate may lead to a loss of sense of self, depersonalization, disturbances of ego and identity, perception of the outside world as alien and uncontrollable/incomprehensible, as well as to social alienation. These should lead to attempts to explain such an incoherent world, and a delusional framework might be just such an attempt (e.g., Jaspers et al. 1959; Bowers 1974; Maher 1974; Miller 1984; Anscombe 1987; Shaner 1999).

Finally, a note is in order with regard to the most prominent symptom of psychosis, hallucinations (Breier and Berg 1999; Epstein et al. 1999), which are apparently associated with DA hyperfunction since they are most efficiently treated by D_2 antagonists (Breier and Berg 1999). While the present model can accommodate the development of delusions, it does not relate at all to hallucinations. However, as pointed out by Epstein et al. (1999), in schizophrenia hallucinations are related to concurrent delusions, and both were shown by these authors to be associated with altered blood flow in the ventral striatum, medial temporal, and frontal regions, i.e., in the limbic circuit. Indeed, Epstein et al. suggested that hallucinations and delusions result from disrupted balance between frontal and temporal inputs to the ventral striatum, which is normally used for maintaining a coherent stream of goal-directed behavior, and that this imbalance leads to aberrant representations of the external

world. Thus, it is possible that the disruption of routine goal-directed behavior stemming from distorted processing in the limbic split circuit as described here could lead also to hallucinations.

In sum, we have suggested that dysregulation of mesolimbic DA in schizophrenia culminates in a dissociation between the activity of the limbic, associative, and motor basal ganglia–thalamocortical split circuits. This dissociation may provide the neurophysiological basis for the "splitting of mental faculties" which is conveyed in Bleuler's (1911) name schizophrenia, and has retained a central position in leading recent formulations of the psychopathology of this disorder (e.g., Frith 1992; Zec 1995; Andreasen et al. 1996, 1999; Graybiel 1997; Friston 1998). In addition, the present proposition, that schizophrenia symptomatology results from the effects of DA dysregulation on both the direct and indirect pathways, implies that the full understanding of the action of APDs, as well as the development of new drugs, should take into account their effects on both pathways. An ideal antipsychotic treatment should normalize the functioning of both pathways.

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