Developmental Pathology, Dopamine, and Stress: A Model for the Age of Onset of Schizophrenia Symptoms

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Abstract

It is unknown why the onset of schizophrenia is typically during late adolescence or early adulthood. The fact that numerous brain maturational processes normally occur during this age period has led researchers to postulate how such processes may be related to the onset of symptoms. To help elucidate the question of age of onset, we selectively review schizophrenia-associated abnormalities of dopamine and related systems, including glutamate and hypothalamic-pituitary-adrenal systems; relevant models of pathophysiology; and the systems' developmental aspects. Based on current findings and conceptualizations, a model is then proposed in which, during adolescence, interactive pathological and normal adolescence-associated processes trigger a positive feedback system that results in a rapid increase in pathology that is proposed to underlie the development of active psychotic symptoms during late adolescence or early adulthood.

Keywords: Schizophrenia, age of onset, dopamine, glutamate, HPA axis, development.


It is well established that onset of the positive symptoms of schizophrenia is typically in late adolescence or early adulthood. However, the pathological changes that cause the syndrome to develop during this time are unknown. Understanding such processes would likely yield important information about the etiology and pathophysiology of this disorder (DeLisi 1992; Pogue-Geile 1997). Dopaminergic dysfunction has long been implicated in the pathophysiology of schizophrenia, although its precise role is unclear (for review, see Willner 1997). Normal brain maturational processes occurring during adolescence, including those involving dopamine (DA) and DA-related systems, have led researchers to hypothesize about how such processes and/or disruptions of such processes may be related to typical schizophrenia age of onset (Weinberger 1987; Walker and Diforio 1997; Keshavan 1999; Finlay 2001; Walker and Bollini 2002). Because of the likely but unclarified role of DA in the pathophysiology of schizophrenia and the potential involvement of the developmental aspects of DA and related systems in the timing of onset, a review of the potential schizophrenia-associated pathophysiology and developmental features of these systems may help elucidate why the disorder appears when it does. Thus, we selectively review such findings and relevant models of pathophysiology and then propose a model that attempts to integrate the pertinent findings and speculations to account for the typical timing of illness onset.

Age of Onset in Schizophrenia

The onset of schizophrenia is generally defined as the age at which symptoms and signs relevant to the diagnosis of schizophrenia begin. Although this is conceptually straightforward, the estimation of this time point is complicated by the often insidious onset of negative symptoms (DeLisi 1992). Further obscuring the identification of illness onset is the occurrence in most preschizophrenia individuals of a prodromal period during which nonspecific and attenuated positive symptoms emerge before the full-blown psychotic symptoms develop (Parnas 1999; der Heiden and Hafner 2000; Cornblatt 2002). Symptoms of such prodromes, which can occur months to years before the full onset of the syndrome, often include depression, increased anxiety, difficulties in concentrating, changes in cognition and perceptions, distrust, social withdrawal, anhedonia, and deterioration of functioning (Parnas 1999; der Heiden and Hafner 2000). Despite these methodological issues, decades of research examining schizophrenia onset have clearly demonstrated that schizophrenia symptoms tend to emerge in late adoles-
DA, DA-Related Systems, and Schizophrenia

History of the DA Hypothesis of Schizophrenia. The notion that DA dysfunction is involved in schizophrenia emerged in the 1960s and was indirectly supported and propelled forward by two sets of findings: (1) drugs that increase DA activity, such as amphetamine, can induce psychotic symptoms in individuals who do not have schizophrenia (Angrist and Gershon 1970; see Krystal et al. 1999) and exacerbate psychotic symptoms in some schizophrenia patients at doses that do not produce psychosis in controls (Janowsky et al. 1973); and (2) drugs that effectively reduce psychotic symptoms are DA receptor antagonists (Carlsson and Lindqvist 1963), and their clinical potency is strongly correlated with their ability to block DA D₂-like receptors (Creese et al. 1976; Seeman et al. 1976). Such findings led to the “classic” DA hypothesis, which stated that schizophrenia results from excessive DA activity (Matthysse 1974; for reviews, see Davis et al. 1991; Grace 1993; Willner 1997; Angrist et al. 2001).

Despite intense research efforts driven by this hypothesis, investigators have been unable to demonstrate a basal hyperdopaminergic state in schizophrenia (Davis et al. 1991; Willner 1997; Soares and Innis 1999). For example, assessing whether DA turnover is increased in the brains of schizophrenia patients by measuring levels of homovanillic acid (HVA, which is the major DA metabolite in primates) has been fraught with methodological difficulties (Willner 1997; Byne et al. 1999) and has yielded variable findings, with some studies suggesting reduced rather than increased HVA levels in schizophrenia patients (Bowers 1974; Pickar et al. 1984; for meta-analysis, see Tuckwell and Koziol 1993). Overall results of these studies suggest that DA turnover or baseline DA levels are not increased in the brains of patients (for review, see Davis et al. 1991; Willner 1997; Byne et al. 1999). Such results contrast with the 35-fold increase in extracellular DA levels associated with acute amphetamine administration (Sharp et al. 1987). Moreover, imaging studies reveal that DA D₂-like receptor occupancy occurs almost immediately after the administration of an antipsychotic agent (Farde et al. 1986), whereas maximum therapeutic effects of such drugs are not observed until after several weeks of administration (Johnstone et al. 1978; Pickar et al. 1984; for discussion, see Sedvall et al. 1986). Such findings undermine the position that the therapeutic effects of agents arise directly from their acute blockade of excess DA at D₂ receptors (Pickar et al. 1984; Sedvall et al. 1986). In addition, DA receptor blockade has been demonstrated in patients who are administered but fail to therapeutically respond to antipsychotic drugs (Wolkin et al. 1989). Furthermore, some investigators have found evidence that DA agonists, which can elicit positive symptoms of schizophrenia, can actually ameliorate negative symptoms in some patients (Angrist et al. 1982; Laruelle et al. 1996; for review, see Willner 1997). Taken together, such results have led many investigators to conclude that schizophrenia symptoms are likely not the result of a simple excess of DA activity (for discussion and reviews, see Davis et al. 1991; Grace 1991, 2000; Willner 1997; Byne et al. 1999; West and Grace 2001).

Overview of Current Findings and Hypotheses of the Role of DA in Schizophrenia

DA turnover, receptors, and release in schizophrenia. Although studies of HVA levels in patients failed to demonstrate increased baseline DA levels, overall they did suggest that DA was indeed somehow associated with schizophrenia symptoms. For example, even though patients' HVA levels were not higher than controls', several studies demonstrated that patients' HVA levels were positively correlated with symptom severity (Davis et al. 1985; Pickar et al. 1986; Davidson and Davis 1988; for review, see Davis et al. 1991).

Another approach to assessing DA involvement in schizophrenia has been the measurement of DA receptor characteristics and functioning in this disorder. As antipsychotic drugs' potency is related to their actions at DA D₂-like receptors (Creese et al. 1976; Seeman et al. 1976), these types of receptors have been the primary target of receptor research in this field. The dorsal and ventral striatum of the basal ganglia receive ascending projections from major DA cell groups of the midbrain (primarily the substantia nigra pars compacta and the ventral tegmental area [VTA], respectively); these striatal regions have a rich supply of D₂-like receptors and thus...
have been the focus of many such investigations (Soares and Innis 1999). Based on their comprehensive meta-
alysis of 20 postmortem and 17 in vivo reports, Kestler et al. (2001) concluded that a subgroup of schizophrenia
patients seem to have elevated numbers of striatal DA D₂-like receptors. The implications of there being increased
striatal D₂-like receptors in schizophrenia patients never exposed to antipsychotic medication (e.g., Wong et al.
1986) are not completely clear, however. Research has indicated that DA cell activity is regulated by homeostatic
mechanisms (Martres et al. 1977; Scatton and Worms 1978; Grace and Bunney 1985a, 1985b; Angulo et al.
1991); one such mechanism is the upregulation (i.e., increase in number) of DA receptors in response to chroni-
cally decreased DA receptor stimulation and downregulation in the presence of chronically increased DA levels.
Thus, although these findings support the concept of aberrant DA functioning in schizophrenia, rather than support-
ing a hyperdopaminergic position, increased D₂-like receptors may actually suggest an upregulation of postsyn-
aptic receptors possibly produced by reduced dopaminergic levels in this region, as several authors have dis-
cussed (Grace 1991; Byne et al. 1999).

Relatively fewer binding studies of D₂-like receptors in extrastriatal regions have been conducted because of the
measurement complications associated with the small numbers of D₂-like receptors found in such areas compared to
the striatum (Soares and Innis 1999). Relative to D₂-like receptors, however, the DA D₁ receptor is in rich supply in
the human neocortex (Hall et al. 1994), and several investigations have assessed D₁ receptor binding in the prefrontal
cortex (PFC) of schizophrenia patients. Methodological issues have complicated such investigations (for discus-
sion, see Abi-Dargham et al. 2002; Weinberger and Lalulle 2002), and studies have produced conflicting results (e.g.,
Knable et al. 1996; Okubo et al. 1997). Recent work by Abi-Dargham et al. (2002), however, suggests that schizo-
phrenia may be associated with increased numbers of D₁ receptors in the dorsolateral PFC (DLPFC).

Using recently developed in vivo neurochemical imaging methods, several researchers have obtained results that suggest
an association between greater amphetamine-induced striatal DA release and schizophre-
ia (Laruelle et al. 1996; Breier et al. 1997; Laruelle and
Abi-Dargham 1999). Importantly, Laruelle and Abi-
Dargham (1999) found that the transient amphetamine-
induced exacerbation of positive symptoms observed in a
subgroup of antipsychotic medication-free schizophrenia
patients was positively correlated with their index of
amphetamine-induced DA release (postamphetamine radi-
oligand displacement from D₂-like receptors relative to
baseline). In addition, results suggested that patients in
an acute phase of their illness, including first episode neu-
roleptic-naive patients, had a significantly greater degree
of amphetamine-induced DA release compared to patients
considered to be in remission. Furthermore, in contrast to
the acutely ill patients, the latter group did not display a
greater degree of apparent amphetamine-induced DA
release compared to controls. Taken together, these find-
ings suggest that amphetamine-induced DA release is ele-
vated in a subgroup of schizophrenia patients and that this
increased DA response seems to be present during active
phases, but not remission, of the illness. Notably, such
findings support the supposition that elevated DA trans-
mission at striatal D₂-like receptors is somehow involved in
the experiencing of psychotic symptoms in schizophrenia
(Laruelle and Abi-Dargham 1999). The correspon-
dence between elevated striatal DA transmission in acute
phase schizophrenia and the findings of increased striatal
D₂ receptors described above may be puzzling at first.
However, when considered in the light of recent models
suggesting a compartmentalization of DA function (Grace
1991), as described below, the possible congruity of such
findings is more apparent.

PFC and mesocortical DA activity in schizophre-
ia. Behavior, neuroimaging, and neuropathology data
support a role for PFC dysfunction in schizophrenia (for
review, see Weinberger et al. 1994). For example, schizo-
phrenia patients display neuropsychological deficits in
domains related to PFC function, including attention,
working memory, and executive functioning (Weickert
and Kleinman 1998). Furthermore, schizophrenia patients
display abnormal activation in regions of the PFC when
performing PFC-related cognitive tasks (Weinberger et al.
1988; Rubin et al. 1991; Berman et al. 1992; Callicott et
al. 2000), and some structural neuroimaging studies have
documented reduced frontal lobe volumes in patients
compared to controls (Breier et al. 1992; Andreasen et al.
1994; Turetsky et al. 1995). Cytoarchitectural abnormali-
ties of the PFC also have been demonstrated in patients
with schizophrenia, including lower PFC levels of the
presynaptic marker synaptophysin, suggesting that
patients as a group have fewer synaptic contacts in this
region (Perrone-Bizzozero et al. 1996; Glantz and Lewis
1997) and decreased neuronal size (Rajkowska et al.
1998; for review, see Harrison 1999).

These putative PFC abnormalities have led numerous
researchers to explore how cortical dysfunction might
relate to DA functioning in schizophrenia (see Weinberger
One approach has focused on the mesocortical DA sys-
tem, which comprises DA neurons that originate in the
VTA and project to the PFC (e.g., Byne et al. 1999; Finlay
2001), and how a dysfunction in this system may influ-
ence subcortical DA functioning (e.g., Weinberger 1987;
Davis et al. 1991).
DA actions in the PFC are complex (Weickert and Kleinman 1998). DA projections from the VTA interact with both the glutamatergic pyramidal cells and local GABAergic interneurons of the PFC. Research suggests that DA modulates pyramidal cell excitability via direct actions on pyramidal neurons (Goldman-Rakic et al. 1989) and indirectly via interneurons (Sesack et al. 1995; for reviews and discussion, see Weickert and Kleinman 1998; Goldman-Rakic 1999; Goldman-Rakic et al. 2000; Grace 2002). It has been shown that PFC DA activity plays a critical role in the cognitive functioning mediated by this region, such as working memory (see Murphy et al. 1997; Goldman-Rakic 1998; Goldman-Rakic et al. 2000). For example, experimentally reducing DA input to the PFC (Brozoski et al. 1979) or injecting a D1 antagonist into the PFC (Sawaguchi and Goldman-Rakic 1991) results in decreased working memory performance in nonhuman primates.

Research has implicated abnormalities in prefrontal dopaminergic functioning in schizophrenia, with many (but not all) findings suggesting reduced DA activity in this region (Akil et al. 1999; for review, see Byne et al. 1999; Finlay 2001). For example, Akil et al. (1999) found that DA axon density in the PFC was significantly reduced in schizophrenia patients. Furthermore, decreased cerebrospinal fluid HVA levels have been associated with reduced task-associated PFC activation, or hypofrontality, in patients (Weinberger et al. 1988). The findings that DA agonists, such as amphetamine, increase regional cerebral blood flow in the PFC and improve cognitive performance in schizophrenia patients (Daniel et al. 1991) are also consistent with the link between hypofrontality and reduced PFC DA activity (for discussion, see Davis et al. 1991). Additionally, deficits induced in rats and nonhuman primates via disruptions to mesoprefrontal DA activity are similar to those of schizophrenia patients (e.g., working memory deficits; Jentsch et al. 1997b; for review, see Finlay 2001).

Numerous findings have also suggested that prefrontal DA may play a role in regulating subcortical DA activity (for review, see Davis et al. 1991). For example, Pycock et al. (1980) found that in rats, chemical lesions of mesoprefrontal DA terminals enhanced responsivity of the subcortical DA system as assessed both behaviorally (i.e., locomotor activity) and biochemically in the striatal region, including the nucleus accumbens. Furthermore, enhancing monoaminergic activity in the PFC via DA agonists was found to reduce subcortical DA release (Kolachana et al. 1995). Seeking to reconcile such findings with those suggesting PFC dysfunction, decreased prefrontal DA activity, and the long-observed link between increased DA activity and worsening psychotic symptoms in schizophrenia, several researchers have posited that the DA abnormalities of the disorder comprise both hypo- and hyperdopaminergia and that prefrontal dysfunction may result in elevated subcortical DA transmission (Weinberger 1987; Davis et al. 1991; Grace 1991). For example, Davis et al. (1991) and Weinberger (1987) have proposed that diminished DA activity in the PFC is specifically related to the negative and cognitive symptoms of the disorder and that this cortical dopaminergic deficit results in increased subcortical DA activity, which is thought to be related to the positive symptoms of the disorder.

DA-Related Systems Implicated in Schizophrenia. It is clear from the above review that the notion of too much or too little DA in schizophrenia is inadequate to explain its role in the disorder. Accumulating findings implicating the involvement of numerous brain regions and other neurotransmitter systems in schizophrenia have led researchers to expand their scope of inquiry to other systems that may also interact with DA (Willner 1997), such as the glutamate system and the HPA axis. Such an approach has led to an emphasis on abnormalities in DA system regulation rather than on a primary DA defect (Weinberger 1987; Grace 1991).

Glutamate, DA, and schizophrenia. In addition to afferents from the DA system and other brainstem regions, the striatal complex receives extensive excitatory glutamatergic input from all areas of the cortex. The limbic ventral striatum in particular receives prominent input from limbic cortical regions (figure 1), including the hippocampus, the amygdala, and the medial frontal cortex (McGeorge and Faull 1989; for review, see Heimer et al. 1995).

Based on several findings, glutamate dysfunction has been strongly implicated in schizophrenia (Olney and Farber 1995; Jentsch and Roth 1999; Goff and Coyle 2001). Especially compelling is the observation that antagonists of the N-methyl-d-aspartate (NMDA) receptor subtype of glutamate, such as phencyclidine (PCP) or ketamine, when administered to healthy humans, produce behavioral and cognitive effects that closely resemble the positive, negative, and cognitive symptoms of schizophrenia (e.g., Adler et al. 1999; Vollenweider et al. 2000); and when administered to stabilized patients, induce a reemergence of idiosyncratic schizophrenia symptoms (e.g., Malhotra et al. 1997; for review, see Olney and Farber 1995; Jentsch and Roth 1999; Goff and Coyle 2001). NMDA receptor antagonists, then, are thought to produce effects that more closely mimic the symptoms of schizophrenia than DA agonists, which generally elicit behavioral effects that resemble only the positive and disorganized aspects of the syndrome. Such observations have led to the hypothesis that reduced glutamate activity at the
NMDA receptor is associated with the disorder (Olney and Farber 1995; Jentsch and Roth 1999). Indeed, chronic abuse of PCP has been observed to produce severe and chronic psychotic symptoms that resemble schizophrenia to a greater extent than those elicited by a single dose of ketamine (for reviews, see Jentsch and Roth 1999; Goff and Coyle 2001). Likewise, PCP abuse in humans has been associated with decreased activation in various cortical areas, including the frontal cortex (Hertzman et al. 1990), and repeated administration of PCP to nonhuman primates has been shown to result in cognitive deficits that are similar to those observed in schizophrenia (e.g., perseveration, behavioral disinhibition) and that can be ameliorated by the atypical antipsychotic drug clozapine (Jentsch et al. 1997a). Findings suggest that the dysfunction associated with chronic PCP administration may arise at least in part from PCP effects on frontal cortical DA functioning (for discussion, see Jentsch and Roth 1999). For example, repeated PCP administration has been shown to reduce DA turnover in the PFC (in nonhuman primates, Jentsch et al. 1997a; in rats, Jentsch et al. 1997b, 1998).

The glutamatergic dysfunction model of schizophrenia is further supported by findings of alterations in both NMDA and non-NMDA receptors in patients (Harrison 1999; Meador-Woodruff and Kleinman 2002). Moreover, clinical trials suggest that agents that facilitate glutamate transmission at the NMDA receptor (e.g., glycine, partial glycine agonists) may modestly improve negative (Javitt et al. 1994; Heresco-Levy et al. 1999) and possibly cognitive symptoms of schizophrenia in patients also receiving antipsychotic medication (Farber et al. 1999; Tsai and Coyle 2002).

As noted above, several findings have suggested that cortical activity is involved in regulating subcortical DA functioning. Cortical glutamatergic output can regulate DA activity by several means, including via projections onto DA neurons and GABAergic interneurons of the midbrain, and interactions with DA terminals in the striatum (for review, see Moore et al. 1999; Grace 2002). As reviewed in detail elsewhere (Moore et al. 1999; West and Grace 2001), findings suggest that corticostriatal glutamatergic projections regulate striatal DA activity via direct and indirect interactions with DA terminals. For
example, manipulations that augment glutamate release in the striatum, such as stimulation of the PFC or hippocampus or application of glutamate agonists to the striatum or accumbens, can result in increased striatal tonic DA release that is not dependent solely on firing of DA neurons (tonic DA release; Grace 1991, 2002; West and Grace 2001). On the other hand, manipulations that antagonize glutamate transmission at the NMDA receptor potentiate striatal phasic DA release, which is dependent on DA cell burst firing (amphetamine- and stress-induced release inferred by hyperlocomotion after subchronic PCP administration to rats, Jentsch et al. 1998; amphetamine-induced DA release after 4-hour sustained administration of ketamine to humans, Kegeles et al. 2000; and after chronic administration of PCP to rats, Balla et al. 2001). Such findings point to the important regulatory role of cortical glutamatergic activity on striatal DA functioning (see Moore et al. 1999; West and Grace 2001). DA can also modulate glutamate transmission at the level of the nucleus accumbens. For example, it has been shown that D₂-mediated DA activity has a tonic attenuating effect on the prefrontal excitatory input received by accumbens neurons (O’Donnell and Grace 1994; West and Grace 2002). In this way, DA seems to wield a modulatory influence on the striatal output driven by prefrontal input.

**Tonic/phasic model and information processing at the level of the nucleus accumbens.** Based on evidence of cortical modulation of subcortical DA activity, a model of DA functioning in schizophrenia has been proposed (Grace 1991, 1993) that is compatible with both the hyper- and/or hypodopaminergic functioning and reduced glutamate activity at the NMDA receptor suggested in this disorder. This model posits that there are two modes by which DA is released in the striatum: phasic DA release, which is the transient high-amplitude release that results when the DA cell fires bursts of action potentials (burst firing) in response to behaviorally relevant stimuli; and tonic DA release, which is dependent on slow tonic DA neuron spike firing (Grace et al. 2003), is proposed to be modulated by corticostratial glutamatergic input, and largely drives extracellular DA concentrations. It is thought that because of its transient nature and rapid removal from the synaptic cleft by the DA transporter, phasic DA release contributes little to baseline extrasynaptic DA levels and is not likely to trigger compensatory mechanisms within the DA system (figure 2A). In contrast, the slower tonic DA release underlies extracellular DA levels (figure 2B). The concentrations of this extracellular DA are too low to stimulate postsynaptic DA receptors (Grace 2002) but are sufficient to stimulate presynaptic DA autoreceptors located on DA terminals that inhibit DA synthesis and release (Grace 1991, 1993, 2002). In this way, tonic DA may control the responsivity of the DA system and thus regulate the magnitude of the phasic DA response that occurs upon DA neuron burst firing in response to behaviorally relevant stimuli. Because corticostratial glutamatergic input is proposed to modulate tonic DA release, this model holds that glutamatergic input to the striatum, such as via prefrontal and/or limbic cortical afferents, is involved in the dynamic modulation of the phasic DA release that occurs in response to DA burst firing (figure 2C; Grace 1991).

This model posits that the prefrontal and/or limbic cortical abnormalities associated with schizophrenia underlie a reduction in cortical glutamatergic input to the striatum, resulting in a persistent reduction in tonic DA release. This would attenuate DA autoreceptor stimulation, which, as follows from above, would drive a pathological potentiation of DA cell burst firing–mediated phasic DA release (figure 3). Such a dysregulation of DA release in the ventral striatum and the resulting increased phasic responsiveness of the system might thereby underlie the positive symptoms of schizophrenia, which is congruent with the pharmacological observations linking psychosis with hyperdopaminergic functioning (e.g., psychotomimetic properties of DA agonists). Also consistent with the model are (1) findings of increased amphetamine-induced (phasic) striatal DA release in patients (e.g., Laruelle and Abi-Dargham 1999); (2) recent work suggesting both an increase in striatal D₂ receptors and an increase in intrasynaptic D₂ DA receptor stimulation in patients experiencing either a first episode or symptom exacerbation (Abi-Dargham et al. 2000); (3) research supporting the hypothesized relation between prefrontal dysfunction and potentiated striatal DA responsivity (Bertolino et al. 1999; Meyer-Lindenberg et al. 2002); and (4) the proposal that antipsychotic drugs exert their therapeutic actions not simply via acute blockade of ventral striatal DA receptors (which could be overcome by similar homeostatic mechanisms as those described above) but by maintained feedback excitation of DA neurons, which would lead to inactivation of phasic DA cell firing via depolarization block (Grace and Bunney 1986; Grace et al. 1997).

As noted above, DA in the nucleus accumbens exerts a modulatory influence on corticoaccumbens glutamatergic projections. With its rich glutamatergic afferents from various cortical regions, the accumbens is positioned to integrate prefrontal and limbic input under the influence of its dense DA afferents from the midbrain (see O’Donnell and Grace 1998). Because activation of the inhibitory accumbens neurons by cortical excitatory input disinhibits thalamic projections to the PFC via the prefrontal-striato-pallido-thalamic circuit (figure 1), accumbens activity serves an important role in modulating feedback activity that the PFC receives from these.
Figure 2. The tonic/phasic model of DA functioning

(A) Phasic DA transmission

1. Burst firing

DA

(DAT) D2

Burst firing

Phasic DA release is the transient, high-amplitude release that occurs when the DA cell fires bursts of action potentials (1) in response to behaviorally relevant stimuli. A large amount of DA (circles) is released into the synaptic cleft and stimulates postsynaptic D2-like receptors (triangles; 2) but then is rapidly removed by the DAT (3), allowing little to escape into the extrasynaptic space. (B) Tonic DA release depends on slow tonic DA neuron firing (1) and is thought to be modulated in part by glu input from the cortex that stimulates glu receptors located on DA terminals (2). Low levels of DA are released into synaptic cleft, which are less affected by DAT (3) than the higher concentrations of phasic DA release; thus, some of this DA overflows into the extrasynaptic space (4). Small amounts of DA are also released at nonsynaptic release sites (5). These sources of DA establish extracellular levels (6). (C) Extracellular DA, established via tonic DA release (1), stimulates the DA autoreceptors that inhibit DA synthesis and release (2). In this way, it is thought that tonic DA activity normally dampens the phasic DA release (3) that occurs in response to behaviorally relevant stimuli (Grace 1991, 1993, 2002; Grace et al. 2003).

Note.—DA = dopamine; DAT = dopamine transporter; glu = glutamatergic; D2 = D2 receptors.
It is proposed that in schizophrenia, reduced glutamatergic corticostriatal input results in a persistent reduction in extracellular DA levels, which diminishes DA autoreceptor stimulation (1). The resulting loss of autoreceptor-mediated inhibition of DA synthesis and release would increase the phasic responsiveness of the system (2) and thus pathologically potentiate stimulus-driven phasic DA release (3).

cortical-subcortical loops (O’Donnell and Grace 1998). Grace and colleagues (Grace et al. 1998; O’Donnell and Grace 1998; Grace 2000; West and Grace 2001) have postulated that the proposed subcortical DA dysregulation associated with schizophrenia might in part underlie disruptions of this crucial modulation at the level of the accumbens and that the resulting alterations in information flow and thalamic regulation of the PFC may be involved in producing the symptoms of the disorder.

In addition to dysregulation of the DA system, abnormalities in hippocampal input to the nucleus accumbens may disrupt modulation of prefrontal throughput (Grace et al. 1998; Grace 2000; West and Grace 2001). Research has suggested that the hippocampus exerts a gating influence over PFC throughput at the level of the accumbens by driving subsets of accumbens neurons into their active, “up” states; only accumbens neurons in the up state can generate spikes in response to PFC input (figure 1; Grace et al. 1998). In this way, the context-dependent information arriving via the ventral hippocampus (Jarrard 1995) can selectively gate accumbens neurons to respond to PFC input based on the relevance of the input to the current context. This would provide a selective reinforcing of accumbens-ventral pallidal-thalamocortical circuits based on the organism’s current situation. The DA system is thought to act in conjunction with the hippocampus in modulating striatal responses in a way that is most appropriate to the current context (see O’Donnell and Grace 1998). Essentially, such a system could keep an organism focused on a specific task while ignoring irrelevant and distracting stimuli.

Numerous findings have implicated hippocampal pathology in schizophrenia, including reduced hippocampal volume (Suddath et al. 1990; Breier et al. 1992; Phillips et al. 2002), functional abnormalities (for review, see Meyer-Lindenberg et al. 2002), and cytoarchitectural abnormalities (for review, see Harrison and Eastwood 2001). Deficits in hippocampal functioning could result in an interruption of context-dependent hippocampal shaping of prefrontal throughput (Grace et al. 1998; O’Donnell and Grace 1998; Grace 2000). Furthermore, the amygdala, which seems to be capable of inducing the active state in accumbens neurons for very brief periods, may have an “unchecked” influence on these neurons in the face of reduced hippocampal input; such an increase in amygdalar influences without the context-dependent hippocampal gating might result in gating of inputs based primarily on their affective valence rather than their relevance to task (hippocampus) or goal-directed behavior (PFC). Such a condition might be related to the positive
symptoms of schizophrenia (see Grace 2000; West and Grace 2001). Interestingly, DA agonists (O’Donnell and Grace 1996) and PCP, both of which can induce psychotic symptoms, disrupt the transitioning of accumbens neurons into their active state (see Grace et al. 1998; Grace 2000).

HPA axis, DA, and schizophrenia. In the face of perceived threat or challenge, numerous systems elicit physiological and behavioral changes (Sánchez et al. 2001) to help the organism respond adaptively to a stressor (McEwen 1998). The actions of the HPA axis, one of the major mediating systems of the physiological stress response, are initiated when the organism is presented with a stressor. Specifically, in response to stressful stimuli, the pituitary gland to release adrenocorticotropic hormone (ACTH), which stimulates the adrenal cortex to synthesize and secrete glucocorticoids, or “stress hormones” (cortisol in primates and corticosterone in rats), which effect physiological changes that facilitate mobilization of bodily resources in the face of the stressor (as reviewed in Walker and Diforio 1997; Bremner and Vermetten 2001; Sánchez et al. 2001).

Prolonged exposure to stress and concomitant physiological stress responses are reported to affect bodily and brain functioning in numerous ways (see McEwen 1998). The hippocampus is one of several brain regions that contain glucocorticoid receptors and is believed to play an important role in the negative feedback system that modulates HPA axis activity (Sapolsky et al. 1990). It has been shown that chronic and excessive exposure to glucocorticoids can lead to structural changes in the hippocampus, including dendrite atrophy (see Sapolsky 2000, for review) and hippocampal cell loss (Sapolsky et al. 1985). Such hippocampal damage can be associated with disruptions in its normal inhibitory effects on HPA axis activity and cognitive impairment (for review, see McEwen 1998; Höschl and Hajek 2001). For example, disorders characterized by chronic elevations of cortisol (e.g., Cushing’s syndrome) are associated with hippocampal volume reduction and deficits in memory performance (for review, see Höschl and Hajek 2001).

Schizophrenia has long been associated with stressful life events (e.g., Brown and Birley 1968). The literature on stress and schizophrenia indicates that stressor exposure is associated with the reemergence and worsening of symptoms (for review, see Norman and Malla 1993). The existing literature on HPA axis functioning in schizophrenia suggests that aberrant responses of this system may be associated with the disorder (for review, see Walker and Diforio 1997; Altamura et al. 1999). For example, several studies have documented increased baseline cortisol levels in patients compared to controls (Lammers et al. 1995; Möck-Šeler et al. 1999), although this has not been consistently observed. HPA axis functioning in schizophrenia has also been assessed via the dexamethasone suppression test (DST), which is thought to assess the integrity of the feedback system of the HPA axis. Although findings have been mixed, a number of studies have suggested that such feedback mechanisms are disrupted in at least a subgroup of schizophrenia patients (e.g., DST combined with CRH exposure, Lammers et al. 1995; for review, see Walker and Diforio 1997; Altamura et al. 1999). Studies of biological responses in patients after stressor exposure have yielded mixed results and underscore how different stressors produce varying HPA responses (Elman et al. 1998; Jansen et al. 2000; for review, see Altamura et al. 1999). Patient heterogeneity in symptom and medication status might be contributing to the mixed findings in this literature, as both can affect cortisol measures (Walker and Diforio 1997; Cotter and Pariante 2002). As Jansen et al. (2000) discussed, abnormal HPA axis responses seem to characterize patient groups, although with the present state of the literature, it is difficult to draw firm conclusions about the nature of such abnormalities.

As Walker and Diforio (1997) discussed, the association between stress exposure and symptom exacerbation and evidence of aberrant HPA functioning in some patients suggest that the HPA system is interacting with neural mechanisms associated with schizophrenia. Based on findings of hippocampal abnormalities in schizophrenia and the prominent role of the hippocampus in HPA axis regulation, investigators have postulated that there may be an association between the hippocampal abnormalities and HPA axis dysregulation observed in some patients (Walker and Diforio 1997; Altamura et al. 1999; Cotter and Pariante 2002). It has been suggested that DA–HPA system interactions may play a role in symptom exacerbation or expression in patients (Finlay and Zigmond 1997; Walker and Diforio 1997). In addition to increasing glucocorticoid levels, acute stress exposure increases DA synthesis and release (Thierry et al. 1976; Abercrombie et al. 1989; Castro and Zigmond 2001). Findings show that the HPA axis contributes to this stress-induced increase in DA activity (Imperato et al. 1989). Stress-induced increases in DA turnover in the rat brain are greatest in the PFC, smaller in the nucleus accumbens, and smaller still in the neostriatum (e.g., Abercrombie et al. 1989; Imperato et al. 1989; Finlay and Zigmond 1997). Studies by Finlay and colleagues suggest that stress-induced increases in mesoprefrontal DA inhibit subcortical DA responses to stress, possibly via an action on PFC glutamatergic efferents, and thus may contribute to the differential responses to stress among the DA systems (Deutch et al. 1990; King et al. 1996). Accordingly, it has been argued that DA turnover in the periventricular nucleus of the hypothalamus, the site of corticotropin-releasing hormone (CRH) synthesis, is increased as a result of stressor exposure (see Walker and Diforio 1997; Altamura et al. 1999). The existing literature on HPA axis functioning in schizophrenia suggests that aberrant responses of this system may be associated with the disorder (for review, see Walker and Diforio 1997; Altamura et al. 1999). For example, several studies have documented increased...
Based on these findings, it has been suggested that a reduction in cortical DA activity such as that possibly associated with schizophrenia may result in a compromised regulation of mesoaccumbens DA neurons, causing them to be hyperresponsive to stress (Finlay and Zigmond 1997; King et al. 1997; Harden et al. 1998; Moore et al. 2001b). It has been shown that disruptions of PFC DA innervation result in decreased tonic activity of VTA DA neurons (Harden et al. 1998). Thus, via the mechanisms described earlier (Grace 1991), such augmented phasic DA responses to stress could be driven by the decreased tonic DA levels that have been proposed to be present in schizophrenia. Such potentiated stress responses in mesoaccumbens DA neurons may thereby contribute to the long-observed relation between increased stress exposure and symptom exacerbation in schizophrenia. Breier et al. (1993) found that schizophrenia patients had greater increases in plasma HVA levels compared to controls after exposure to acute metabolic stress. Furthermore, they found that reduced PFC volume was associated with greater stressor-induced HVA increases in patients. As Breier et al. noted, such findings are consistent with the hypothesis that schizophrenia is associated with a dysregulated subcortical DA response to stress that is secondary to PFC dysfunction.

Research suggests that exposure to a chronic stressor may result in a decrease or downregulation of the tonic activity of VTA DA neurons (e.g., chronic cold stressor; Moore et al. 2001b); such an effect should result in decreased tonic DA levels in the nucleus accumbens (Grace et al. 2003). Thus, it is possible that exposure of patients to chronic stress, including the stress that is likely to be associated with experiencing certain schizophrenia symptoms, could further exacerbate the subcortical DA dysregulation that is proposed to occur in this disorder.

Drawing from studies of the interactions among DA, glutamate, the hippocampus, and the HPA axis, Walker and Diforio (1997) proposed a "neural diathesis-stress" model that attempts to explain some of the key features of schizophrenia, including typical age of onset. Specifically, they postulate that some individuals who develop schizophrenia are hypersensitive to DA because of striatal DA receptor abnormalities. Because of augmented activity of the HPA axis during adolescence, individuals with such a preexisting sensitivity to subcortical DA may experience a pathological potentiation of subcortical DA transmission around this age period. Such enhanced DA activity and possible hippocampal damage in these individuals may further increase HPA axis activity, with the augmentation of HPA axis activity in turn resulting in further abnormalities in both DA and hippocampal functioning. According to this model, such a sequence of events may result in adolescent onset of schizophrenia because of the increases in HPA axis activity thought to take place during this period.

As elaborated further at the end of this article, we have integrated such system-based hypotheses into a model based on the triggering of a positive feedback system during adolescence that may underlie a rapid increase in pathology during this age period; such an age-related process is hypothesized to contribute to the timing of typical onset of schizophrenia symptoms. For example, given recent data showing that the PFC exerts a suppressive effect over sensory-mediated activation of the basolateral amygdala (BLA; Rosenkranz and Grace 2000, 2001), another consequence of PFC dysfunction in schizophrenia may be an inability of the PFC to suppress inappropriate emotional responses to stimuli (Rosenkranz and Grace 2000, 2001). Thus, it is proposed that in addition to a potential hyperresponsivity to stress, hippocampal damage, and a consequent increased susceptibility to the damaging effects of stressor exposure, some individuals who develop schizophrenia may also have a hyperactivation of the BLA secondary to PFC dysfunction. It is possible that such a hyperactivated BLA would, via its projections to the central amygdala-hypothalamic pathway (Pitkanen et al. 1997), dysregulate the HPA axis as well, potentially driving further hippocampal damage and HPA axis dysregulation (figure 4). Indeed, such an active pathological process may help to explain why delays in the initiation of antipsychotic drug treatment are associated with worse outcome (McEvoy et al. 1991; Loebel et al. 1992; Szymanski et al. 1996).

Summary of Evidence Regarding DA and DA-Related System Abnormalities in Schizophrenia. Although the classic DA hypothesis has proven inadequate to explain DA dysfunction in schizophrenia, evidence has consistently indicated that this neurotransmitter has a role in the disorder. The correspondence between DA activity and symptom expression has gained support via recent neuroimaging findings that suggest an association between greater amphetamine-induced striatal DA release and acute phase schizophrenia (Laruelle and Abi-Dargham 1999). Findings to date have also suggested that schizophrenia may be associated with decreased DA activity in the mesocortical system, which may be related to PFC dysfunction and cognitive impairments observed in patients. It has been proposed that DA dysfunction may be characterized by both hypo- and hyperdopaminergia and that PFC dysfunction may drive subcortical DA dysregu-
Developmental Aspects of DA and Related Systems and Implications for Schizophrenia Age of Onset

The putative schizophrenia-associated brain abnormalities that are suggestive of disruptions in early brain development (Harrison and Eastwood 2001) and the disorder’s tendency to have an onset during a period of continued brain maturation (i.e., adolescence) have led researchers to examine ways in which normal brain maturational processes and/or their disruptions may be related to the pathophysiology of this disorder (e.g., Feinberg 1982; Woods 1998).
DA

**Normal development of DA systems.** Studies that seek to characterize DA system development typically investigate age-related changes in various indexes of DA system functioning in humans, nonhuman primates, and rodents. This review focuses on human and nonhuman primate studies that included the developmental period of adolescence and young adulthood.

**Mesocortical DA system.** Although full characterization of the age-related alterations of the mesocortical system during adolescence is hampered by the limited number of developmental studies that span late childhood through early adulthood, existing literature suggests that the role of DA in PFC functioning changes significantly during this developmental period (Lewis 1997; Spear 2000). Primate studies have generally suggested that cortical DA functioning tends to increase through adolescence (Goldman-Rakic and Brown 1982; Rosenberg and Lewis 1995). Rosenberg and Lewis (1995) found that DA fiber innervation and varicosity density of the PFC in rhesus monkeys peaked during adolescence, followed by a substantial decline. Lidow and Rakic (1992) found a preadolescent peak in the density of D2 and/or D1 receptors in the PFC that was followed by a decline by adolescence to stable adult levels.

**Subcortical DA systems.** Numerous investigations have examined and described postnatal developmental changes in subcortical DA system functioning, although primate studies that encompass the adolescent age period are relatively few and have tended to yield somewhat inconsistent results. Meng et al. (1999) found that in humans, presynaptic DA uptake sites, or DA transporters, of the striatum increased in density from infancy to late childhood (ages 9–10), at which time their density remained constant through at least 16 years of age. DA transporters are expressed at the DA axon terminal (Cooper et al. 1996), and thus changes in their density are thought to reflect changes in DA synaptic density (Moll et al. 2000). Studies of humans have reported declines in striatal D1 receptor density beginning during infancy (Meng et al. 1999; Montague et al. 1999). However, whereas Montague et al. observed continuous decreases in density from infancy to adulthood, Meng et al. found that D1 densities did not consistently decline after 6 to 8 months of age. Meng et al. found a similar but later-occurring pattern of age-related changes in striatal D2 receptors: D2 density peaked between infancy and childhood and then declined by ages 9 to 10 years to reach relatively stable levels. Thus, in humans, subcortical D1 and/or D2 receptor densities decline early in postnatal development.

**Functional implications of findings.** DA activity in the PFC is known to play a critical role in the cognitive functioning mediated by this region (Goldman-Rakic 1999). Furthermore, research shows that adolescence is characterized by continued improvement in performance up to adult levels in many of the cognitive domains thought to involve DA functioning in the PFC, such as working memory, abstract reasoning, and suppression of context-irrelevant information and responses (e.g., Levin et al. 1991; Welsh et al. 1991; Luna et al. 2001; for review and discussion, see Lewis 1997; Luna and Sweeney 2001). Observations regarding adolescence-associated increases of mesoprefrontal DA activity that parallel cognitive performance have led researchers to postulate that the crucial modulatory role of DA on PFC functioning may be changing in significant ways during this period (Benes et al. 1996; Lewis 1997; Spear 2000). GABAergic interneurons in the PFC regulate pyramidal cell activity, and excitatory axon collaterals of pyramidal cells synapse onto both other pyramidal cells and inhibitory interneurons; thus, pyramidal cells not only shape the activity of other pyramidal cells but also modulate their own activity via interactions with GABAergic neurons (Lewis 1997). As Lewis postulated, such interactions may help maintain the appropriate balance between excitatory and inhibitory activity for intact information processing in the PFC. As noted earlier, PFC DA activity modulates both GABAergic and glutamatergic cell activity; such modulation appears to be critical for the cognitive functioning mediated by the PFC. As reviewed by Lewis (1997), a marked decline in both prefrontal glutamatergic synapses and certain indexes of inhibitory input of GABAergic neurons appears to begin during adolescence as part of the marked “pruning” of synapses that occurs in late childhood and adolescence (Huttenlocher and Dabholkar 1997) and is thought to contribute to the developing efficiency of the neocortex (Keshavan et al. 1994; Spear 2000). Based on the temporal relations of age-related changes in glutamatergic, GABAergic, and mesoprefrontal DA, Lewis (1997) postulated that the increased modulatory activity by the mesoprefrontal DA system during adolescence may be especially crucial for intact prefrontal functioning because of these other changes in prefrontal cortical circuitry.

Conclusions regarding the functional implications of possible adolescence-associated alterations in subcortical DA functioning are more difficult to draw. Based on current findings, some researchers have speculated that subcortical DA activity is reduced in adolescence relative to adulthood (Spear 2000), whereas others have postulated that DA transmission is elevated during this age period (e.g., Bolanos et al. 1998). Furthermore, as Spear (2000) pointed out, age-related changes in subcortical DA functioning, which is regulated by powerful homeostatic mechanisms and apparently influenced by mesoprefrontal...
DA activity, may reflect compensatory adjustments that occur in response to developmental changes in other systems (e.g., the mesocortical DA system).

**Normal DA development, schizophrenia-associated abnormalities, and age of onset.** Research suggests that schizophrenia may be associated with decreased mesocortical DA functioning (e.g., Akil et al. 1999) and that such disruptions may be related to PFC dysfunction and cognitive impairments that characterize the disorder. These observations have led researchers to speculate that schizophrenia may be associated with abnormalities in the normal adolescence-associated development of the mesocortical DA system and that such disruptions might be associated with the tendency of this disorder to have an onset in late adolescence (e.g., Weinberger 1987; Finlay 2001). The findings implicating decreased prefrontal DA activity in schizophrenia are certainly consistent with the hypothesis that the adolescence-associated expansion of mesocortical DA influence is disturbed in the disorder. It has been suggested that the potential pathological consequences of such disturbances may be amplified by other age-related changes that are occurring in the PFC (e.g., reduced glutamatergic synapses and GABAergic influence; Lewis 1997). As noted earlier, such disruptions in the mesocortical DA system and corresponding PFC dysfunction would set the stage for the pathological dysregulation of subcortical DA functioning (Weinberger 1987; Davis et al. 1991; Grace 1991) that has been hypothesized to occur in schizophrenia and to be associated with the positive symptoms of the disorder.

In light of the accumulating findings that suggest early brain abnormalities in the disorder (for reviews, see Walker 1994; Turner et al. 1997) and given the late developmental stage in which alterations in this system continue to occur, it is possible that modifications of mesocortical DA systems that potentially contribute to onset may be a consequence of maladaptive changes produced in response to pathology occurring much earlier in development, such as early hippocampal pathology, the relevant findings of which we selectively review below.

**Early Limbic Damage, PFC Dysfunction, and DA Dysregulation.** Several findings have suggested that hippocampal dysfunction is associated with schizophrenia (Suddath et al. 1990; for review, see Harrison and Eastwood 2001). Intriguing findings have emerged regarding the potential role of early hippocampal pathology in PFC dysfunction and related dysregulation of subcortical dopaminergic functioning in schizophrenia. Lipska and colleagues (e.g., Lipska et al. 1993, 1995; Al-Amin et al. 2001) have demonstrated that lesioning the ventral hippocampal region of neonate rat pups results in behavioral abnormalities that are thought to reflect increased mesolimbic DA activity (Lipska et al. 1993) and do not manifest until the rats reach early adulthood. Also, they have found that as adolescents and adults, neonatally lesioned rats display increased motor hyperactivity in response to the psychotomimetic NMDA antagonist MK-801 (Al-Amin et al. 2001), impaired performance on prepulse inhibition (Lipska et al. 1995) and working memory tasks as adults, and impaired social behavior both before puberty and as adults (see Lipska et al. 1999). These rats also appear to exhibit an increased response to stress. Specifically, as early adults they displayed hyperactivity after exposure to swim stress and saline injection (a stressor) compared to controls (Lipska et al. 1993). Such an upregulated response to stress is not observed in rats lesioned in the ventral hippocampal region as early adults (see Lipska et al. 1993, 1994), suggesting that neonatally induced hippocampal damage may influence the mesolimbic DA response to stress. In contrast, adult lesions to the medial prefrontal cortical region in rats produce similar, although transient, hyperactivity after saline injection, suggesting that such a manipulation results in short-term amplification of the mesolimbic DA stress response (see Lipska et al. 1993, 1994). Thus, it is thought that the delayed behavioral effects of neonatal ventral hippocampal lesions, some of which have been observed in schizophrenia (e.g., apparent increased responsivity to stressors, deficits on prepulse inhibition and working memory tasks, impaired social behavior in both childhood and adulthood), are mediated by disruptions that have been hypothesized to be present in the disorder, as described earlier (e.g., prefrontal dysfunction, increased responsivity of mesolimbic DA system, impaired prefrontal modulation of stress-induced response of subcortical DA activity).

In recent studies, Grace and colleagues (see Grace and Moore 1998; Grace 2000; West and Grace 2001) have integrated and expanded Lipska and colleagues' findings into work examining a rodent model of schizophrenia pathophysiology. Specifically, to induce cytoarchitectural abnormalities to the hippocampus, entorhinal cortex, and PFC that resemble the cytoarchitectural changes that have been associated with schizophrenia, the mitotoxin methyl azoxymethanol acetate (MAM) was administered during specific time periods of prenatal development to rats in utero (see Grace and Moore 1998; Grace 2000; West and Grace 2001). Consistent with the findings of Lipska and colleagues, these rats, as adults, displayed increased activity in response to novelty (Moore et al. 2001a), hyperactivity in response to PCP and amphetamine, and deficits in prepulse inhibi-
tion (Ghajarnia et al. 1998). Furthermore, electrophysiological studies revealed that in MAM-treated rats there was a loss of the hippocampal gating of nucleus accumbens cells that normally regulates accumbens cell responsiveness to PFC input; instead, there were abnormal influences of the amygdala on accumbens cell stimulation (Grace and Moore 1998; Grace 2000) that suggested that early limbic damage results in reduced hippocampal modulation of accumbens activity and an amplified and possibly pathological influence by the amygdala (Grace 2000). In addition, the modulatory influence of DA on glutamatergic pyramidal cells of the PFC was reduced in MAM-treated compared to control rats (Lavin and Grace 1997). Such early lesion-induced disruptions in functioning might come about by alterations in the organization of the cortical-subcortical system and its modulation by DA that result from attempts of the system to compensate for its loss of regulatory influence of the hippocampus (Grace 2000).

Recent work by Bertolino et al. (1999) has extended this early-lesion paradigm to primates. They assessed neuronal integrity via N-acetylaspartate (NAA) levels and striatal DA concentrations in rhesus monkeys, some of which had undergone ablation of several limbic structures, including the hippocampus and amygdala. Greater neuronal pathology of the DLPFC, as indicated by reduced NAA, was associated with decreased basal DA levels in the striatum. Furthermore, Bertolino et al. (1999) found that increased DLPFC neuronal pathology was related to increased phasic DA release in the striatum in response to amphetamine infusion directly into the DLPFC. This research group has obtained results suggesting the same associations between NAA-assessed prefrontal pathology and measures of subcortical tonic and phasic DA release in schizophrenia patients (Bertolino et al. 1999). These results are consistent with other reports (Lipska et al. 1993; Grace 2000) in suggesting that a state of prefrontal dysfunction arising via developmental disruptions in limbic cortical regions induces subcortical DA dysregulation.

Glutamate System. Several lines of research have implicated glutamate dysfunction, and specifically NMDA receptor hypofunction, in schizophrenia (Goff and Coyle 2001). Research has demonstrated that the psychotomimetic effects of NMDA receptor antagonists (e.g., ketamine), as well as their neurotoxic effects, are age-dependent in that they do not typically produce schizophrenia-like symptoms in children but do induce such effects once individuals reach late adolescence or early adulthood (Farber et al. 1995; Duncan et al. 1999). Thus, maturational processes occurring during adolescence are likely related to the onset of psychotomimetic properties of NMDA receptor antagonists and thus may be related to schizophrenia pathophysiology (Farber et al. 1995; Duncan et al. 1999). Farber et al. (1995) have speculated that late-adolescent maturational changes in the glutamate system increase the demand of NMDA receptor-mediated modulation of excitatory activity in the cortex via their facilitation of GABAergic neuron activity. If these receptors are hypofunctional during this period, these authors postulate, then structural damage may result because of the loss of NMDA receptor action and resulting neurotoxic effects of overstimulation, and such damage may be related to the onset of psychosis. Other researchers have speculated that the process of synaptic elimination that largely affects glutamatergic synapses and occurs during adolescence (Duncan et al. 1999) may be related to schizophrenia age of onset (e.g., Feinberg 1982). For example, Keshavan et al. (1994) suggest that the pruning of glutamatergic synapses that occurs in late childhood and adolescence may be excessive in schizophrenia and that such a pathological process may be related to the adolescent onset of this disorder.

HPA Axis

Normal development of the HPA axis. Adolescence, which is characterized by a myriad of changing expectations, opportunities, and potential threats, is associated with increased exposure to stressors as well as an increase in the perception of stress (Spear 2000, for review). In addition, human HPA axis functioning is reported to increase during adolescence (Kiess et al. 1995; Walker et al. 1996; see Spear 2000), although the relevant data are less clear in humans compared to rodents (Spear 2000). For example, cortisol levels are reported to gradually increase through middle childhood (e.g., Gandia et al. 1990), followed by a possibly more rapid increase during adolescence (Kiess et al. 1995; for review, see Walker et al. 1996, 2001). Some research has also suggested that HPA axis responsivity, although more difficult to assess in humans, may be augmented during this period (see Spear 2000).

Normal HPA axis development, schizophrenia-associated abnormalities, and age of onset. As Walker and DiForio (1997) proposed, the increased HPA axis activity that putatively occurs during adolescence may contribute to the tendency of the onset of schizophrenia to occur during this age period. One possibility is that adolescence-associated increases in stressor exposure along with a possible increase in HPA axis hyperresponsivity may, in individuals with preexisting prefrontal and/or limbic cortical pathology and HPA axis abnormalities, trigger a positive feedback system of increasing pathology involving further hippocampal, HPA, and PFC dysfunction; such processes, as follows from above, would lead to
further PFC dysfunction and subcortical DA dysregulation and thus possibly the onset of psychotic symptoms.

### Positive Feedback Model of Stress-Driven Development of Schizophrenia Pathophysiology

As reviewed above, a particularly compelling set of findings with regard to the question of age of onset of schizophrenia symptoms are those describing the delayed-onset behavioral and physiological manifestations of early disruptions to hippocampal and limbic cortical functioning (e.g., see Lipska et al. 1993; Grace 2000). The resulting abnormalities map in an impressive way onto abnormalities that have been demonstrated or proposed to occur in schizophrenia. The possibility that some degree of limbic and possibly prefrontal cortical dysfunction as modeled by this early lesion work (Lipska et al. 1993; Moore et al. 1999; Grace 2000) is present in individuals before overt symptom onset is congruent with the observations of behavioral, cognitive, and social impairments in some pre schizophrenia children (e.g., lower IQ scores, attention deficits, increased social isolation; for review, see Davies et al. 1998). Furthermore, in schizophrenia patients, cytoarchitectural abnormalities in both the hippocampal region and the PFC have been detected that are consistent with the proposal that there are disruptions in the early development of these regions (for review, see Harrison and Eastwood 2001). However, how this relates to the adolescent or adult onset of the resulting abnormalities is unclear; that is, if similar early limbic cortical pathology is indeed present in individuals who later develop schizophrenia, why does the severe functional decline seen with age of schizophrenia onset typically not occur until adolescence? It is possible that such early pathology may be present in at least some pre schizophrenia individuals but that the severe functional consequences (e.g., reduced mesocortical DA functioning, subcortical DA dysregulation) do not emerge until adolescence because of the changing demands of or need for the modulatory influence of mesocortical DA and the cortical regulation of subcortical DA that may occur during this age period. It is hypothesized that such changes and their interaction with preonset pathology that may occur during adolescence trigger a positive feedback loop of increasing pathology that ultimately leads to full onset of the schizophrenia syndrome. Based on recent work using gene expression microarrays, Mirmics et al. (2001) have proposed that a preexisting impairment of PFC synaptic transmission may be a precipitating factor in disrupting the system further during subsequent adolescence-associated synaptic pruning. It is possible that such abnormalities and resulting pathology as described in their “disease of the synapse” model (2001) may in part underlie the preonset PFC pathology that is proposed to predispose the system to the later pathological processes involved in the model delineated here.

As postulated by Lewis (1997) and described earlier, developmental changes occurring in the PFC around the time of adolescence (e.g., reduction of GABAergic influence and pruning of glutamatergic synapses) may increase the demand for the modulatory influence of mesoprefrontal DA activity. With normal DA system development, such an increase in demand would be met by the continued augmentation of the mesoprefrontal DA system that occurs during this age period. In individuals with limbic and possibly PFC dysfunction (Lipska et al. 1993; Moore et al. 1999; Grace 2000) who later develop schizophrenia, however, there might be a disruption in this expansion of mesocortical DA system function during adolescence (Weinberger 1987; Finlay 2001)—possibly at the very time when there is an increased demand for its intact and increased functioning. One possibility is that the resulting inadequacy of mesocortical DA activity in individuals with early limbic cortical pathology may initiate or further exacerbate preexisting disruptions in PFC functioning. It is also possible that a subgroup of preonset individuals may exhibit a delayed pathology within limbic or PFC systems as a consequence of disruptions in mesocortical DA system development (as described in figure 4). Such states may characterize preschizophrenia individuals in early or middle adolescence, before the onset of active prodromal or overt psychotic symptoms, or individuals at increased risk for developing schizophrenia.

Such preonset individuals with impaired mesocortical DA and PFC functioning would also likely display deficits in subcortical DA regulation (Weinberger 1987; Grace 1991). As described earlier, stress-induced increases in DA activity are normally most apparent in the PFC, and it is thought that such activity may dampen subcortical DA responses to stress (Finlay and Zigmond 1997). Recent work by Syss et al. (1999) has suggested that this pattern of differential responsibility to stress among the DA systems does not emerge until around adolescence, as the PFC becomes more mature. Specifically, in preadolescent rodents (postnatal day 10 or 18), the predominant DA response to stressor exposure occurred subcortically, whereas in midadolescent and adult rodents (postnatal day 45 and 100), the largest DA response to stress was observed in the PFC (Syss et al. 1999). Increases in both HPA axis responsivity and actual stressor exposure that are thought to characterize adolescence are likely to add to the increased burden of the mesocortical DA system during this age period because of the dual role of this system in activating the PFC during stress exposure and reg-
ulicating the subcortical DA response to stress. The findings of Syss et al. (1999) suggest that adolescence-associated maturational processes of the PFC, such as the enhancement of mesocortical DA activity, may work to increasingly regulate the subcortical DA response to stress during this age period. Thus, the possible disruptions in mesocortical DA that may be present in preschizophrenia individuals during this period would likely result in dysregulated mesoaccumbens DA responses to stress as these individuals move into adolescence. In addition, research suggests that schizophrenia patients may have HPA axis hyperresponsivity. It is possible that such hyperactive HPA responses are also present in at least a subset of preschizophrenia individuals; such a condition may further exacerbate the potentially dysregulated subcortical DA responses to HPA axis activity and stress. Furthermore, as noted earlier, such dysregulated subcortical DA would likely disturb the critical modulation of information flow that normally occurs via DA activity in the nucleus accumbens, which would likely contribute to PFC dysfunction and result in information processing abnormalities.

As noted earlier, before overt psychosis onset, most individuals who develop schizophrenia experience a period of prodromal symptoms, including depression, anxiety, social withdrawal, and perceptual disturbances (see Parnas 1999). It is possible that such individuals who have experienced disruptions in the development of the mesocortical DA system, PFC dysfunction, possible HPA axis hyperresponsivity, and increasingly dysregulated subcortical DA secondary to such disruptions as described here would begin to display the behavioral and cognitive impairments that characterize the prodrome (figure 4). Such speculations of an association between decreased mesocortical activity and prodromal symptoms, including negative symptoms, are congruent with the hypothesis that negative symptoms are associated with decreased cortical DA activity (Weinberger 1987; Davis et al. 1991; O’Donnell and Grace 1998). Moreover, the hypothesis that HPA axis abnormalities are present before onset is consistent with the observation that high-risk individuals who go on to develop psychosis display higher levels of anxiety and depressive symptoms than those who do not develop frank psychosis (E.C. Johnstone, personal communication, 2003).

What factors might contribute to the transition of at least a subset of such individuals from the prodrome to the psychotic stage of the disorder? It is likely that, in addition to the normative increase in stressor exposure during adolescence, individuals with prodromal symptoms actually experience increased distress as a result of their prodromal symptoms. For example, such individuals may experience social isolation and/or rejection that may be secondary to the distrust, anxiety, social awkwardness, perceptual abnormalities, and overall deterioration in functioning that may occur during the prodrome. As noted above, chronic stressor exposure may downregulate the tonic activity of VTA DA neurons (Moore et al. 2001b). Thus, it is possible that such increased stressor exposure, which may in part be driven by the prodrome, could perpetuate and worsen the prodrome by resulting in further subcortical DA dysregulation via the mechanisms described earlier (figure 4).

It is also possible that various coping mechanisms appear before and/or during the prodromal phase as a means of compensating for suboptimal processing abilities and that these coping mechanisms may also exacerbate the pathological process described here. For example, Weinberger et al. (1993, 1994) have suggested that in schizophrenia, the hippocampus may be inappropriately recruited during working memory tasks because of PFC dysfunction. Recent work has corroborated such findings in suggesting that during increased working memory demands, schizophrenia patients show both hypofrontality and increased activity in temporal regions, including the hippocampus, compared to controls (Meyer-Lindenberg et al. 2001; see Berman 2002). As noted above, adolescence is typically characterized by continued improvement in cognitive domains such as working memory. Thus, it is possible that in such individuals with compromised PFC functioning and consequent aberrant activity in the hippocampus, the increased working memory demands of adolescence may place a heightened burden on the hippocampus during this time that may contribute, along with other pathological processes described here, to hippocampal vulnerability to damage. Pantelis et al. (2003) recently reported that when preschizophrenia high-risk (for schizophrenia) patients were assessed before the development of active psychotic symptoms, they outperformed high-risk individuals who did not develop psychosis on a verbal paired associates test, an explicit memory task that involves the hippocampus. This finding may reflect differences in the propensity of the two groups in the level of recruitment of the hippocampus. For example, one possibility is that high-risk individuals who do not develop psychosis have an impaired ability to recruit the hippocampus and thus perform more poorly on such tasks. This impaired ability to recruit the hippocampus may protect individuals who do not go on to develop psychosis, as they may thus be less likely to inappropriately enlist the hippocampus during other types of cognitive demands in the face of PFC pathology. In contrast, the high-risk individuals who go on to develop psychosis may be better able to appropriately employ the hippocampus during such tasks, but as a consequence they may be more vulnerable to hippocampal overrecruiting during tasks typi-
cally mediated by the PFC. Such increased hippocampal demand, when combined with an augmented HPA axis–driven release of glucocorticoids, could further exacerbate hippocampal pathology. Dysfunction within the PFC may also result in other pathological processes, such as disrupted PFC suppression of inappropriate emotional responses of the BLA (Rosenkranz and Grace 2000, 2001). In addition to increasing stress because of hyperresponsivity to emotional stimuli, the hyperactivated BLA could result in additional HPA axis dysregulation, as described earlier.

In our model (figure 4), we propose that when a critical subset of the pathological processes (e.g., decreased mesocortical DA functioning, PFC pathology, HPA axis hyperresponsivity, hippocampal pathology, increased demands on the hippocampus due to PFC pathology) and normal adolescence-associated changes (e.g., increased HPA axis responsivity, increased stressor exposure) occur in concert, a positive feedback system is triggered that initiates or exacerbates further pathological processes, such as additional HPA axis activation, glucocorticoid-induced hippocampal damage, and PFC dysfunction. As depicted, we hypothesize that the triggering of such interacting pathological processes leads to the potentiation of phasic DA responses that underlies the development of psychotic symptoms during late adolescence or early adulthood. In a comparison of their high-risk patients, Pantelis and colleagues (Pantelis et al. 2000; Phillips et al. 2002) reported that the high-risk individuals who later developed active psychosis had larger hippocampal volume (similar to the volume of healthy controls) just prior to illness onset when compared to high-risk individuals who did not go on to develop overt psychosis (Phillips et al. 2002). Although clearly speculative, one possible explanation (Phillips et al. 2002) is that the development of psychosis is associated with reduced hippocampal volume before onset (similar to those high-risk individuals who do not manifest psychosis) but is followed by an increase in hippocampal volume just prior to the onset of full-blown psychosis. Based on longitudinal data from a subset of these patients (Pantelis et al. 2000) and findings of decreased hippocampal volume in first episode patients (Phillips et al. 2002), it appears that if there is such an increase in hippocampal volume, it is followed by volume loss during the transition to illness (Pantelis et al. 2000). It is possible that the larger hippocampal volume in prespsychosis high-risk individuals compared to high-risk individuals who do not go on to manifest psychosis could reflect a transient reactive swelling secondary to rapid pathological processes occurring because of the initiation of a positive feedback loop, as described here.

The sequence of pathological events described above may have significant implications for preonset treatment of the disorder. Specifically, treating high-risk individuals with antipsychotic drugs, with their concomitant side effects, may not be the most effective preventive strategy. Alternatively, antianxiety treatments may be more efficacious at reducing or even halting the stress-driven positive feedback loop prior to onset of potentially irreversible pathological changes.

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