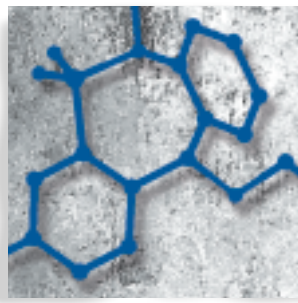


# Pharmacological aspects

## *Dopamine in the history of the schizophrenic brain: recent contributions of brain-imaging studies*

Marc Laruelle, MD; Anissa Abi-Dargham, MD



Recent developments in positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging have enabled functional measurements of dopamine (DA) transmission at dopamine D<sub>2</sub> receptors in the living human brain. Studies using these techniques have demonstrated that, in schizophrenia, increased DA stimulation of striatal D<sub>2</sub> receptors is associated with the first episode of illness and subsequent episodes of illness exacerbation. While this dysregulation of DA function is not associated with the severity of positive symptoms per se, increased synaptic DA activity is predictive of good therapeutic response to antipsychotic treatment. Abnormalities of DA function were not detected during periods of illness remission. These findings are integrated into a clinical model proposing that, in schizophrenia, neurodevelopmental abnormalities of cortico-subcortical connectivity result in a vulnerability of the mesolimbic DA system to the development of a process of endogenous sensitization, and that the resulting sustained hyperstimulation of D<sub>2</sub> receptors induces neuroplastic changes within corticostriatal-thalamocortical loops, perturbing information processing and underlying the psychotic experience.

The “classical” dopamine (DA) hypothesis of schizophrenia proposed that hyperactivity of DA transmission is responsible for the positive symptoms (hallucinations, delusions) observed in this disorder.<sup>1</sup> This hypothesis was supported by the correlation between clinical doses of antipsychotic drugs and their potency for blocking DA D<sub>2</sub> receptors,<sup>2,3</sup> and by the psychotogenic effects of DA-enhancing drugs (for reviews, see references 4 and 5). These critical pharmacological observations suggested, but did not establish, a dysregulation of DA systems in schizophrenia.

On the other hand, negative and cognitive symptoms are generally resistant to treatment by antipsychotic drugs. Impairment in higher cognitive functions, such as working memory, is one of the most enduring symptoms of schizophrenia and a strong predictor of poor clinical outcome.<sup>6</sup> Functional brain-imaging studies suggested that these symptoms are associated with a dysfunction of the prefrontal cortex (PFC).<sup>7-9</sup> Studies in nonhuman primates demonstrated that deficit in DA transmission in the PFC and lack of stimulation of D<sub>1</sub> receptors (the main DA receptor subtype in the PFC) induce cognitive impairments reminiscent of those observed in patients with schizophrenia.<sup>10</sup> Together, these observations suggest that a deficit in DA transmission at D<sub>1</sub> receptors in the PFC might be implicated in the cognitive impairments presented by these patients.<sup>9</sup>

Thus, the current view on DA and schizophrenia proposes that schizophrenia might be associated with a dopaminergic imbalance involving an excess of subcortical DA and a deficit in cortical DA function: subcortical mesolimbic DA projections might be hyperactive (resulting in

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**Author affiliations:** Departments of Psychiatry and Radiology, Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute, New York, NY, USA

**Address for correspondence:** Marc Laruelle, Department of Psychiatry, Columbia University, New York State Psychiatric Institute, 1051 Riverside Drive, Unit 42, New York, NY 10032, USA  
(e-mail: ml393@columbia.edu)

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## Selected abbreviations and acronyms

<b>BP</b>	<i>binding potential</i>
<b>DA</b>	<i>dopamine</i>
<b>DAT</b>	<i>dopamine transporter</i>
<b>DLPFC</b>	<i>dorsolateral prefrontal cortex</i>
<b>DOPA</b>	<i>dihydroxyphenylalanine</i>
<b>GABA</b>	<i>γ-aminobutyric acid</i>
<b>IBZM</b>	<i>iodobenzamide</i>
<b>ICC</b>	<i>intraclass correlation coefficient</i>
<b>LSD</b>	<i>lysergic acid diethylamide</i>
<b>MAM</b>	<i>methylazoxymethanol</i>
<b>α-MPT</b>	<i>α-methyl-para-tyrosine</i>
<b>NAA</b>	<i>N-acetylaspartate</i>
<b>NMDA</b>	<i>N-methyl-D-aspartate</i>
<b>PET</b>	<i>positron emission tomography</i>
<b>PFC</b>	<i>prefrontal cortex</i>
<b>SPECT</b>	<i>single-photon emission computed tomography</i>
<b>VTA</b>	<i>ventral tegmental area</i>

hyperstimulation of D<sub>2</sub> receptors and positive symptoms) and mesocortical DA projections to the PFC might be hypoactive (resulting in hypostimulation of D<sub>1</sub> receptors, negative symptoms, and cognitive impairment).<sup>9,11</sup>

Despite decades of effort to validate these hypotheses, documentation of abnormalities of DA function in schizophrenia has remained elusive. Postmortem studies measuring DA and its metabolites and receptors in the brains of schizophrenic patients have yielded inconsistent or inconclusive results (for a review, see reference 11). The lack of clear evidence for altered dopaminergic indices in schizophrenia might indicate that DA transmission is abnormal only relative to other systems, such as the glutamatergic system.<sup>12</sup> On the other hand, the absence of data supporting the DA hypothesis of schizophrenia might be due to the difficulty in obtaining a direct measurement of DA transmission in the living human brain.

However, over the last few years, progress in brain-imaging methods has enabled direct measurement of DA transmission at the D<sub>2</sub> receptor, and the application of these techniques to the study of schizophrenia has provided new insights into the nature and the role of DA function dysregulation in schizophrenia. This paper will briefly review these data, and explore the implications of these results in terms of pathophysiology and treatment.

## Brain imaging as a tool for measuring DA synaptic activities

Neuroreceptor imaging with positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are classically aimed at measuring neuroreceptor parameters in the living human brain. More recently, several groups have demonstrated that under specific conditions, in vivo neuroreceptor binding techniques can also be used to measure acute fluctuations in the concentration of the endogenous transmitters in the vicinity of radiolabeled receptors.<sup>13-16</sup> Competition between radiotracers and transmitters for binding to neuroreceptors is the principle underlying this technique, though other mechanisms such as agonist-induced receptor internalization might also play a role (for a review, see reference 17). So far, applications of this new paradigm have been developed mainly to study DA transmission at D<sub>2</sub> receptors.

Endogenous competition between DA and radiolabeled D<sub>2</sub> receptor ligands was initially documented in ex vivo studies performed in rodents. Amphetamine, which releases DA and thereby increases endogenous DA synaptic concentration,<sup>18,19</sup> reduced the in vivo binding of the D<sub>2</sub> agonist [<sup>3</sup>H]-*N*-propylnorapomorphine<sup>20,21</sup> and the D<sub>2</sub> antagonist [<sup>3</sup>H]raclopride.<sup>22,23</sup> Reduced in vivo accumulation of D<sub>2</sub> tracers was also reported following pretreatment with the DA uptake inhibitors amfonelic acid and methylphenidate.<sup>21</sup> The opposite effect (ie, increased tracer accumulation) was induced by drugs that decrease DA endogenous concentration, such as reserpine and γ-butyrolactone.<sup>21,23-26</sup>

These interactions suggested that PET and SPECT could be used to measure acute fluctuations in endogenous DA. In baboons, the binding potential (BP) of various dopamine D<sub>2</sub> radiotracers was decreased by drugs that increase DA synaptic concentration, such as amphetamine,<sup>13,14,16,27-30</sup> cocaine,<sup>31</sup> or GBR 12909.<sup>32</sup> Increased radiotracer uptake was observed following drugs that reduce DA availability, such as reserpine<sup>33</sup> or γ-vinyl-γ-aminobutyric acid (γ-vinyl-GABA).<sup>34</sup> These interactions were also reported in humans: decreased specific binding of [<sup>11</sup>C]raclopride or [<sup>123</sup>I]iodobenzamide ([<sup>123</sup>I]IBZM) was reported following acute administration of the DA-enhancing drugs methylphenidate,<sup>35,36</sup> amphetamine,<sup>37,38</sup> cocaine,<sup>39</sup> and even cognitive challenges.<sup>40</sup> Conversely, increased [<sup>123</sup>I]IBZM BP was documented following DA depletion with the reversible tyro-

sine hydroxylase inhibitor  $\alpha$ -methyl-*para*-tyrosine ( $\alpha$ -MPT).<sup>41</sup>

The amphetamine-induced reduction in [<sup>123</sup>I]IBZM or [<sup>11</sup>C]raclopride BP to D<sub>2</sub> receptors has been well validated as an indirect measure of the change in synaptic DA concentration induced by the challenge. The first step was to establish that the amphetamine-induced reduction in radiotracer BP was mediated by DA release, and not by some indirect effect of amphetamine unrelated to DA release. The mediation of the amphetamine effect by DA release was demonstrated by establishing that pretreatment with the tyrosine hydroxylase inhibitor  $\alpha$ -MPT blocked the effect of amphetamine on [<sup>123</sup>I]IBZM BP.<sup>14</sup> More recently, Villemagne et al<sup>42</sup> showed that pretreatment with the dopamine transport (DAT) blocker GBR 12909 (a drug that prevents amphetamine-induced DA release) blocked the effect of amphetamine on [<sup>11</sup>C]raclopride BP. The second step was to study the relationship between the magnitude of DA release and the reduction in radiotracer BP, to assess the potential of the imaging measurement to provide a quantitative measure of DA release. This comparison was accomplished in primates by comparing amphetamine-induced DA release measured with microdialysis and reduction of radiotracer binding measured with PET or SPECT following various doses of amphetamine.<sup>14,38</sup> These studies demonstrated that the reduction in radiotracer BP was linearly correlated with the peak DA release measured with microdialysis. This observation validated the use of this noninvasive paradigm to measure changes in synaptic DA following amphetamine, and provided an operational calibration of the imaging signal. We also evaluated the reproducibility of the SPECT measurement of the amphetamine effect on D<sub>2</sub> receptor BP. We observed an excellent reproducibility of the measurement, both in baboons, where the intraclass correlation coefficient (ICC) was 0.97,<sup>14</sup> and in humans, where the ICC was 0.89.<sup>43</sup> Together, these results supported the feasibility of measuring amphetamine-induced DA release in humans with this noninvasive technique.

### Imaging amphetamine-induced DA release in schizophrenia

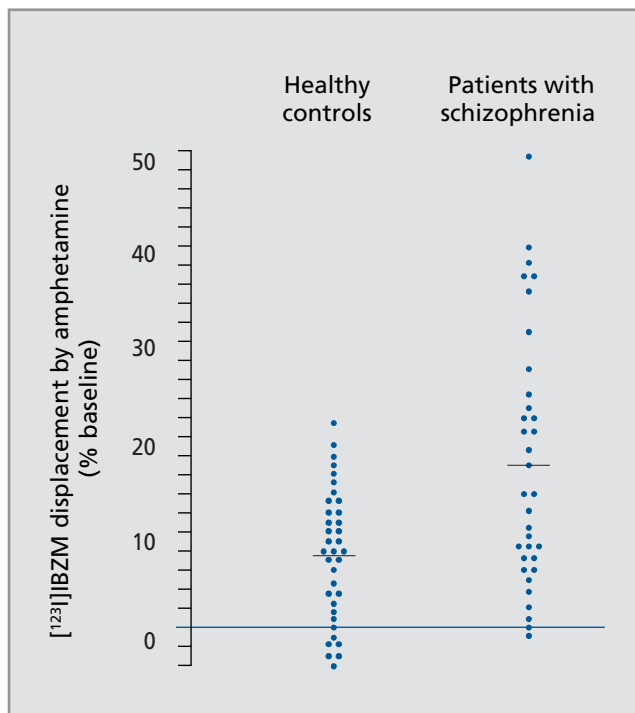
We and others adopted this imaging technique to measure amphetamine-induced DA release in patients with schizophrenia and matched healthy controls.<sup>38,44-46</sup> Our final sample consisted of 34 patients with schizophrenia

and 36 matched healthy controls.<sup>46</sup> Patients met *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)* criteria for schizophrenia, and were carefully screened to exclude any patients with a history of drug or alcohol abuse or dependence. Healthy controls were matched for gender, age, race, and parental socioeconomic status. Patients had been off medication for at least 21 days at the time of the study. Seven were neuroleptic naive, experiencing a first episode of the illness. Patients were recruited under two modalities. Seventeen patients were recruited shortly after admission to the hospital for clinical reasons and were experiencing an episode of clinical deterioration at the time of recruitment. In all cases, the admission was voluntary. The other 17 patients were recruited in outpatient clinics. These patients were in a stable phase of the illness, and were admitted to the hospital only for the purpose of the study. In the control subjects, the amphetamine-induced reduction in [<sup>123</sup>I]IBZM BP was  $7.5 \pm 7.1\%$  ( $n=36$ ). Compared with the controls, the patients with schizophrenia displayed a marked elevation of amphetamine-induced [<sup>123</sup>I]IBZM displacement ( $17.1 \pm 13.2\%$ ,  $n=34$ ,  $P=0.0003$ , *Figure 1*). A similar finding has been reported by Breier et al<sup>38</sup> using [<sup>11</sup>C]raclopride, PET, and a smaller dose of amphetamine (0.2 mg/kg, intravenously). This increased effect of amphetamine on [<sup>123</sup>I]IBZM BP in patients with schizophrenia was not related to differences in amphetamine plasma disposition, since amphetamine plasma levels were similar in both groups. Providing that the affinity of D<sub>2</sub> receptors for DA is unchanged in this illness (see discussion in reference 46), these data are consistent with an increased amphetamine-induced DA release in schizophrenia.

The amphetamine effect on [<sup>123</sup>I]IBZM BP was similar in chronic/previously treated patients ( $16.2 \pm 13.5\%$ ,  $n=27$ ) and first-episode/neuroleptic-naive patients ( $20.9 \pm 12.2\%$ ,  $n=7$ ,  $P=0.41$ ), and both groups were significantly different from controls. In the previously treated group, no association was found between the duration of the neuroleptic-free period and the amphetamine-induced [<sup>123</sup>I]IBZM displacement ( $r=0.02$ ,  $P=0.91$ ). Together, these results indicated that the exaggerated dopaminergic response to amphetamine exposure was not a prolonged side effect of previous neuroleptic exposure.

In patients with schizophrenia, the amphetamine challenge induced a significant increase in positive symptoms. The emergence or worsening of positive symptoms was transient, and patients returned to their baseline

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**Figure 1.** Effect of amphetamine (0.3 mg/kg) on [ $^{123}\text{I}$ ]iodobenzamide ([ $^{123}\text{I}$ ]IBZM) binding in healthy controls and untreated patients with schizophrenia. The y axis shows the percentage decrease in [ $^{123}\text{I}$ ]IBZM binding potential induced by amphetamine, which is a measure of the increased occupancy of dopamine  $\text{D}_2$  receptors by dopamine following the challenge. Increased stimulation of  $\text{D}_2$  receptors in schizophrenia was associated with transient worsening or emergence of positive symptoms.

symptomatology within a few hours of the challenge. We observed a significant correlation between the increase in positive symptoms and the [ $^{123}\text{I}$ ]IBZM displacement ( $r=0.54$ ,  $P=0.0009$ ). This result provides direct evidence that exaggerated activation of DA transmission at  $\text{D}_2$  receptors mediates the expression of psychotic symptoms following amphetamine challenge. However, DA-mediated stimulation of  $\text{D}_2$  receptors explained only about 30% of the variance in the positive symptom changes, indicating that other factors play a role in the exacerbation of these symptoms following amphetamine.

We tested associations between the amphetamine effect on [ $^{123}\text{I}$ ]IBZM BP and several demographic and clinical variables in the group of patients with schizophrenia, in an attempt to characterize the profile of patients with exaggerated response. Symptom severity per se (whether

positive or negative symptoms) at baseline was not predictive of the amphetamine effect on  $\text{D}_2$  receptor transmission. No association was found between the amphetamine effect and age, gender, race, subject socioeconomic status, familial socioeconomic status, duration of illness, or number of previous hospitalizations. However, patients who were experiencing an illness exacerbation (identified by the fact that their admission was motivated by clinical reasons) presented a higher amphetamine-induced [ $^{123}\text{I}$ ]IBZM displacement ( $23.7\pm 13.2\%$ ,  $n=17$ ) than patients who were in remission and recruited as outpatients ( $10.5\pm 9.7\%$ ,  $n=17$ ,  $P=0.002$ ). Furthermore, amphetamine-induced [ $^{123}\text{I}$ ]IBZM displacement in remitted patients ( $10.5\pm 9.7\%$ ,  $n=17$ ) was not statistically different from controls ( $7.5\pm 7.1\%$ ,  $n=36$ ,  $P=0.27$ ). This observation suggests that dysregulation of DA release in patients with schizophrenia might be present only during episodes of illness exacerbation. Studying the same patients during exacerbation and remission phases is required to confirm this point.

An important question raised by these studies is whether the stress associated with psychiatric hospitalization and/or the scanning procedure might account for the excess DA release measured in patients with schizophrenia, since stress activates DA release.<sup>47,48</sup> To investigate this potential confounding factor, we recently studied amphetamine-induced DA release in a group of nonpsychotic unipolar depressed subjects ( $n=9$ ).<sup>49</sup> Patients from both groups (patients with schizophrenia and patients with unipolar depression) were experiencing a severe psychiatric episode, had recently been admitted to the unfamiliar environment of a research ward, and were untreated at the time of the scan. Despite reporting elevated anxiety levels, the patients with depression did not show elevated activation of the DA system by amphetamine (amphetamine-induced displacement of [ $^{123}\text{I}$ ]IBZM in depressed subjects was  $9.8\pm 5.5\%$ , not significantly different from their control subjects,  $7.8\pm 2.5\%$ ,  $P=0.38$ ). This finding supports the hypothesis that the increased amphetamine effect observed in patients with schizophrenia is not a non-specific consequence of stressful conditions (although it could represent a specific interaction between stress and schizophrenia).

The data reviewed above are consistent with higher DA output in the striatum of patients with schizophrenia, which could be explained by increased density of DA terminals. Since striatal DATs are exclusively



localized on DA terminals, this question was investigated by measuring binding of the DAT radioligands [ $^{123}\text{I}$ ]-2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl)tropane ([ $^{123}\text{I}$ ]-2 $\beta$ -CIT)<sup>50</sup> or 2 $\beta$ -carbomethoxy-3 $\beta$ -(4-[ $^{18}\text{F}$ ]fluorophenyl)tropane ([ $^{18}\text{F}$ ]CFT)<sup>51</sup> in patients with schizophrenia. Neither study reported a difference in DAT binding between patients and controls. In addition, Laruelle et al<sup>50</sup> reported no association between amphetamine-induced DA release and DAT density. Thus, the increased presynaptic output suggested by the amphetamine studies does not appear to be due to higher terminal density. This observation is consistent with postmortem studies, which failed to identify alterations in striatal DAT binding in schizophrenia.<sup>52-57</sup>

### Imaging baseline DA activity in schizophrenia

A major limitation of the amphetamine studies is that they measured changes in synaptic DA transmission following a nonphysiological challenge (ie, amphetamine) and did not provide any information about synaptic DA levels at baseline, ie, in the unchallenged state. Measurement of baseline synaptic levels of DA required the development of another imaging strategy. As discussed above, several laboratories reported that, in rodents, acute depletion of synaptic DA is associated with an acute increase in the in vivo binding of [ $^{11}\text{C}$ ]raclopride or [ $^{123}\text{I}$ ]IBZM to D<sub>2</sub> receptors. The increased binding was observed in vivo but not in vitro, indicating that it was not due to receptor upregulation,<sup>41</sup> but to removal of endogenous DA and unmasking of D<sub>2</sub> receptors previously occupied by DA. Based on these preclinical data, an acute DA depletion challenge was developed in humans using  $\alpha$ -MPT, to assess the degree of occupancy of D<sub>2</sub> receptors by DA.<sup>41</sup>

Using this strategy, we studied baseline occupancy of D<sub>2</sub> receptors by DA in patients with schizophrenia compared with healthy control subjects.<sup>58</sup> D<sub>2</sub> receptor availability was measured at baseline (ie, in the absence of any pharmacological intervention) and during acute DA depletion. Acute DA depletion was achieved by administration of high doses of  $\alpha$ -MPT for 2 days.<sup>59,60</sup> Since this duration of treatment is too short to induce detectable D<sub>2</sub> receptor upregulation, the main difference between D<sub>2</sub> receptor availability measured at baseline and in the depleted state is due to the unmasking of D<sub>2</sub> receptors previously occupied by DA.<sup>41</sup> Therefore, comparing

D<sub>2</sub> receptor availability at baseline and in the depleted state provided an indirect measure of the proportion of D<sub>2</sub> receptors occupied by DA in the baseline state. Patients (n=18) and controls (n=18) were matched on age, gender, parental socioeconomic status, cigarette smoking, and weight. Among the 18 patients, 8 were antipsychotic-naïve and experiencing a first episode of illness. All patients were experiencing an episode of acute illness exacerbation.

Removal of endogenous DA by  $\alpha$ -MPT increased D<sub>2</sub> receptor availability by 9 $\pm$ 7% in controls and 19 $\pm$ 11% in patients with schizophrenia ( $P=0.003$ ). The differential effect of  $\alpha$ -MPT between patients and controls was not due to differences in  $\alpha$ -MPT bioavailability.  $\alpha$ -MPT plasma levels were not different in controls (19 $\pm$ 6  $\mu\text{g/mL}$ ) and patients (21 $\pm$ 6  $\mu\text{g/mL}$ ,  $P=0.522$ ). The  $\alpha$ -MPT effect on D<sub>2</sub> receptor availability was not statistically different between drug-naïve (n=8, 17 $\pm$ 6%) and previously treated patients (n=10, 20 $\pm$ 15%), and both groups were significantly different from controls.

Thus, the results of this study suggest that DA occupies a greater proportion of striatal D<sub>2</sub> receptors in patients with schizophrenia compared with matched control subjects during the first episode of illness and subsequent episodes of illness exacerbation. The significance of this result stems from the fact that the paradigm used here reveals D<sub>2</sub> receptor occupancy by DA during the baseline scan, ie, in the absence of any pharmacological intervention. The results of the  $\alpha$ -MPT study are consistent with results of studies reporting rates of dihydroxyphenylalanine (DOPA) decarboxylase activity in patients with schizophrenia, using [ $^{18}\text{F}$ ]DOPA<sup>61-64</sup> or [ $^{11}\text{C}$ ]DOPA.<sup>65</sup> Four out of five studies reported increased accumulation of DOPA in the striatum of patients with schizophrenia, and the combined analysis of these studies yields an effect size of 0.92 $\pm$ 0.45, which is significantly different from zero ( $P=0.01$ ). While the relationship between DOPA decarboxylase and DA synthesis rate is unclear (DOPA decarboxylase is not in the rate-limiting step of DA synthesis), these observations are consistent with the higher synaptic DA concentration observed in patients with schizophrenia in the  $\alpha$ -MPT study.

In patients,  $\alpha$ -MPT significantly reduced positive symptoms, and high baseline DA was predictive of good response of positive symptoms to  $\alpha$ -MPT. However, baseline global severity of positive symptoms was not associated with high DA synaptic concentration at baseline. Among positive symptoms, only severity of

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suspiciousness was associated with a trend toward high synaptic DA levels ( $r^2=0.19$ ,  $P=0.07$ ). This negative result might be due to the limited resolution of the SPECT camera. Considerable preclinical evidence from rodent studies supports the hypothesis that antipsychotic drug action is associated with D<sub>2</sub> receptor antagonism in the mesolimbic (ventral striatal, including nucleus accumbens) rather than the nigrostriatal (dorsostriatal) DA systems (for a review, see reference 66). The limited resolution of the SPECT camera prevented us from distinguishing the respective contributions of the ventral and dorsal striata to the SPECT signal. Studies with a high-resolution PET camera are needed to clarify this point.

On the other hand, this negative result might indicate that the severity of positive symptoms rated cross-sectionally by the Positive and Negative Syndrome Scale (PANSS) depends mostly on factors located downstream from the mesolimbic dopaminergic synapses. The dysfunctional neuronal circuits that underlie the experience of positive symptoms are likely to involve dysregulated prefrontal-ventrostriatal-ventropallidal-mediodorsal-thalamoprefrontal loops, and their regulation by hippocampal and amygdaline afferents.<sup>67,68</sup> The results of the studies reviewed here directly confirm that these loops are under modulatory influence of subcortical DA. A sudden rise in subcortical DA (such as that measured following amphetamine) will exacerbate these symptoms, while a sudden decline in DA (such as measured following  $\alpha$ -MPT) will blunt their intensity. Thus, psychotic symptomatology includes both DA-dependent and DA-independent components, with the respective contributions of each component varying from patient to patient (and presumably varying with time within the same patient).

Fourteen out of the 18 patients agreed to complete the 6 weeks' period of antipsychotic medication as inpatients (4 patients elected to be treated as outpatients and were excluded from the treatment phase of the study). Compared with baseline, a significant decrease in positive symptoms was measured after 6 weeks of treatment ( $P<0.0001$ ). Changes in negative symptoms were not significant. A large between-subject variability was observed in the improvement of positive symptoms at 6 weeks ( $28\pm 16\%$ ). Higher synaptic levels of DA at baseline, as measured by the  $\alpha$ -MPT effect on D<sub>2</sub> receptor BP, were significantly associated with greater improvement in positive symptoms following 6 weeks of antipsy-

chotic treatment ( $r^2=53$ ,  $P=0.0029$ ). Thus, the dysregulation of DA transmission revealed by the imaging study was predictive of better response of positive symptoms to antipsychotic treatment. Schizophrenic patients who experienced positive symptoms in the presence of increased DA stimulation of D<sub>2</sub> receptors showed a remarkable and rapid decline in these symptoms following treatment with antipsychotic drugs. On the other hand, subjects who experienced positive symptoms in the presence of apparently normal stimulation of D<sub>2</sub> receptors by DA showed little improvement in these symptoms following 6 weeks of antipsychotic treatment. The fact that high levels of synaptic DA at baseline predicted a better or faster response to atypical antipsychotic drugs (13 out of 14 patients were treated with atypical drugs) also suggests that the D<sub>2</sub> receptor blockade induced by these drugs remains a key component of their initial mode of action.

Contrary to widely accepted views, antipsychotic drugs have only partial efficacy against positive symptoms. A substantial proportion of schizophrenic patients, possibly a third, remain actively psychotic despite appropriate and prolonged blockade of D<sub>2</sub> receptors.<sup>69,70</sup> The data presented in this study suggest that, in some patients, blockade of D<sub>2</sub> receptors by antipsychotic drugs fails to significantly alter positive symptoms because these symptoms might not be related to excessive stimulation of these receptors by DA.

## Cortical regulation of subcortical DA transmission

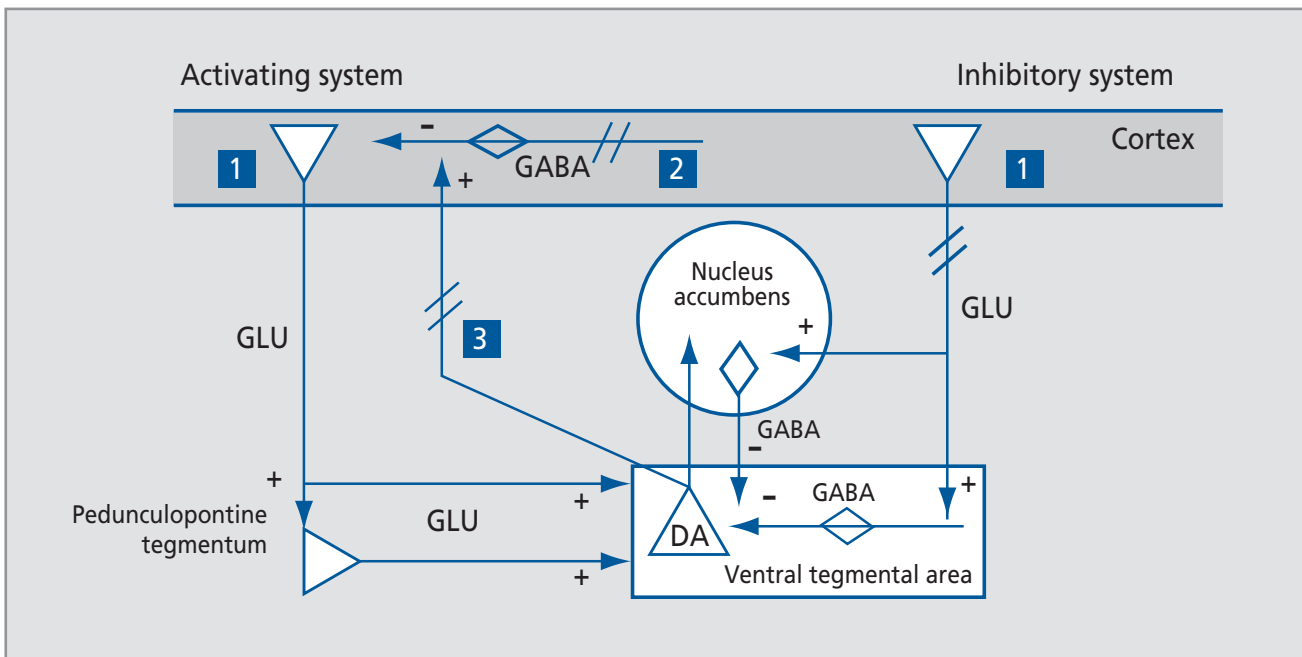
While the studies reviewed above generally confirmed the classical DA hypothesis of schizophrenia, it is important to examine these results in light of the more recent views of schizophrenia as a neurodevelopmental illness, involving dysconnectivity of multiple cortico-subcortical and intracortical networks. While it cannot be definitively ruled out that the DA dysregulation revealed by these studies stems from a primary abnormality of DA neurons, it seems more likely that these abnormalities are a consequence of cortico-subcortical dysconnectivity. Moreover, given the weight of evidence implicating PFC connectivity as a central deficient node in the schizophrenic brain, it is tempting to speculate that a dysregulation of the firing activity of dopaminergic neurons might stem from a failure of the PFC to regulate this process. In fact, it has long been hypothesized that dys-

regulation of subcortical DA function in schizophrenia may be secondary to a failure of the PFC to adequately control subcortical dopaminergic function.<sup>71,72</sup> In patients with schizophrenia, a low *N*-acetylaspartate (NAA) concentration in the dorsolateral prefrontal cortex (DLPFC), a marker of DLPFC pathology, is associated with increased amphetamine-induced DA release.<sup>73</sup> This result provides evidence that disinhibition of subcortical DA activity is associated with prefrontal pathology in schizophrenia.

According to a model introduced by Carlsson,<sup>74</sup> the activity of midbrain DA neurons is under dual influence of PFC via an activating pathway (the “accelerator”) and an inhibitory pathway (“the brake”), allowing fine tuning of dopaminergic activity by the PFC (Figure 2). The activating pathway is provided by indirect glutamatergic projections onto the dopaminergic cells (indirect projections likely involve the pedunculopontine tegmentum<sup>75</sup>). The inhibitory pathway is provided by

glutamatergic projections to midbrain GABAergic interneurons or striatomesencephalic GABAergic neurons. The inhibition of dopaminergic cell firing following amphetamine is an important feedback mechanism by which the brain reduces the effect of amphetamine on DA release. The inhibition of dopaminergic cell firing induced by amphetamine is mediated both by stimulation of presynaptic D<sub>2</sub> autoreceptors, and by stimulation of this inhibitory pathway.<sup>76</sup>

Following administration of amphetamine (ie, under conditions in which the inhibitory pathway should be activated), *N*-methyl-D-aspartate (NMDA) receptor blockade results in a failure of activation of the inhibitory pathway, resulting in exaggerated amphetamine-induced DA release.<sup>77</sup> Kegeles et al<sup>78</sup> recently confirmed this mechanism in humans: pretreatment with the noncompetitive NMDA antagonist ketamine significantly enhanced amphetamine-induced (0.25 mg/kg) decrease in [<sup>123</sup>I]IBZM BP, from -5.5±3.5% under control



**Figure 2.** Model of modulation of ventral tegmental area dopamine (DA) cell activity by the prefrontal cortex (PFC). The activity of midbrain DA neurons is under the dual influence of PFC via activating and inhibitory pathways, allowing fine tuning of dopaminergic activity by the PFC. The activating pathway is provided by glutamatergic projections onto the dopaminergic cells, and the inhibitory pathway is provided by glutamatergic projections to midbrain  $\gamma$ -aminobutyric acid (GABA)-ergic interneurons or striatomesencephalic GABA neurons. See text for description and references. This model predicts that a deficiency in *N*-methyl-D-aspartate (NMDA) transmission (lesion 1) and/or GABA PFC function (lesion 2) and/or DA PFC function (lesion 3) would result in a failure of the PFC to inhibit subcortical DA activity under conditions of excessive stimulation (such as stress or amphetamine challenge). GLU: glutamate.

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conditions to  $-12.8 \pm 8.8\%$  with ketamine pretreatment ( $P=0.023$ ). The increase in amphetamine-induced DA release with ketamine (greater than 2-fold) was comparable in magnitude to the exaggerated response seen in patients with schizophrenia. These data are consistent with the hypotheses that (i) the alteration of DA release revealed by the amphetamine challenge in schizophrenia results from a disruption of glutamatergic neuronal systems regulating dopaminergic cell activity; and (ii) schizophrenia might be associated with NMDA receptor hypofunction.<sup>79-81</sup>

The failure of glutamatergic control of DA release might stem from mechanisms other than NMDA hypofunction. For example, glutamatergic projections from the PFC to the VTA are under tonic inhibition by prefrontal GABA and DA activity (see reference 82 and references therein). It follows that deficits in GABAergic or dopaminergic function in the PFC (both of these deficits are also implicated in schizophrenia) are expected to have similar consequences to an NMDA deficiency on the subcortical DA response to amphetamine. Thus, in patients with schizophrenia, various or multiple mechanisms (NMDA receptor hypofunction, GABAergic or dopaminergic deficits in the PFC) may lead to the dysregulation of subcortical DA revealed by the amphetamine challenge (*Figure 2*).

Moreover, preclinical studies documented that dysregulation of subcortical DA function might be a delayed and enduring consequence of neurodevelopmental abnormalities of limbic-cortical connectivity. Studies in rodents showed that alteration of cortico-limbic development induced by prenatal exposure to the antimitotic agent methylazoxymethanol (MAM) acetate results in increased subcortical DA release in adulthood.<sup>83</sup> The increase in subcortical DA transmission in MAM-treated rodents was correlated strongly with the severity of cerebral cortical thinning resulting from altered development. Adult rhesus monkeys with neonatal ablation of the amygdala-hippocampal formation exhibit lower NAA concentrations in the PFC and impaired PFC inhibition of subcortical DA functions.<sup>84,85</sup>

## Schizophrenia and endogenous sensitization

While the evidence reviewed above is consistent with the model that dysregulation of subcortical DA func-

tion in schizophrenia is an enduring consequence of neurodevelopmental abnormalities involving cortico-subcortical dysconnectivity, this model fails to account for the episodic nature of this dysregulation. In the imaging studies reviewed above, abnormalities of subcortical DA function as revealed by elevated amphetamine-induced DA release was observed in patients experiencing a first episode of illness or an episode of illness exacerbation, but not in patients studied during a period of illness remission.

Neurochemical sensitization of mesolimbic DA systems has been proposed by several authors as one mechanism that might underlie the progression of a “silent” vulnerability into an overt symptomatology, resulting in further “toxic” effects on the brain.<sup>86-90</sup> Sensitization is a process whereby exposure to a given stimulus, such as a drug or a stressor, results in an enhanced response to subsequent exposures. This phenomenon has been well characterized in rodents: repeated exposure to psychostimulants, such as amphetamine, induces an increase in the behavioral (locomotion) and biochemical (DA release) response to amphetamine, other stimulants, or stressors (for reviews, see references 89 and 91–93). Sensitization can be conceived of as a form of learning behavior, but its adaptive value is not apparent. Sensitization is essentially a nonhomeostatic, positive feedback mechanism, and makes individuals more vulnerable rather than more resistant to a number of pharmacological or environmental stimulations.

The brain-imaging data reviewed above provide support for the hypothesis that dysfunction of DA systems in schizophrenia results from a process similar to the sensitization phenomenon described following repeated psychostimulant exposure, because both conditions are associated with increased psychostimulant-induced DA release. Since patients included in the study had not been previously exposed to psychostimulants, the enhanced behavioral (psychotic reaction) and biochemical (DA release) response might result from an “endogenous” sensitization process.

Neurodevelopmental abnormalities associated with schizophrenia may set the stage for the development of an endogenous sensitization process.<sup>88,94</sup> We have reviewed elsewhere<sup>94</sup> the preclinical literature suggesting that early brain lesions that affect the development of cortical connectivity result in enhanced vulnerability to sensitization of mesolimbic DA systems. During late adolescence, the failure of cortical development in schiz-



schizophrenia might limit the capacity of the brain to modulate stress-related increased activity of mesolimbic DA neurons. This failure of normal homeostatic and buffering mechanisms results in an increased vulnerability of DA neurons to the development of a process of endogenous sensitization, a response not observed in humans under normal circumstances. While increased DA activity is initially associated with environmental stressors, the sensitization process is self-perpetuating, and, beyond a given threshold, becomes independent of the environmental factors responsible for its initiation. This positive feedback loop, in which more DA leads to more DA, ultimately results in a clinical episode and in the expression of positive symptoms.

Chronic blockade of D<sub>2</sub> receptors and/or neuroleptic-induced depolarization blockade of dopaminergic neurons might allow a progressive extinction of this sensitized state. This proposition is suggested by the failure to detect an increase in amphetamine-induced DA release in currently untreated patients with schizophrenia during periods of stabilization. However, the high rate of relapse during prolonged treatment discontinuation suggests that this endogenous sensitization process might resume upon environmental, physiological, or pharmacological stress.

### DA hyperactivity, neuroplasticity, and positive symptoms

The data derived from the brain-imaging studies reviewed above are consistent with the hypothesis that subcortical DA transmission mediates the expression of positive symptoms in patients with schizophrenia. However, the data also suggest that a component of the positive symptomatology is independent of increased activity of subcortical DA transmission. First, as discussed earlier, the increase in DA transmission at striatal D<sub>2</sub> receptors following amphetamine explained only 30% of the variability in the psychotic response to *d*-amphetamine. Second, the severity of positive symptoms was not associated with increased synaptic DA concentration as revealed by the  $\alpha$ -MPT challenge. Thus, a simple relationship between intensity of DA transmission at the D<sub>2</sub> receptors and severity of positive symptoms is an oversimplification.

In addition, such a simple relationship is not supported by the delay between D<sub>2</sub> receptor blockade and antipsychotic response, or by resistance of positive symptoms to

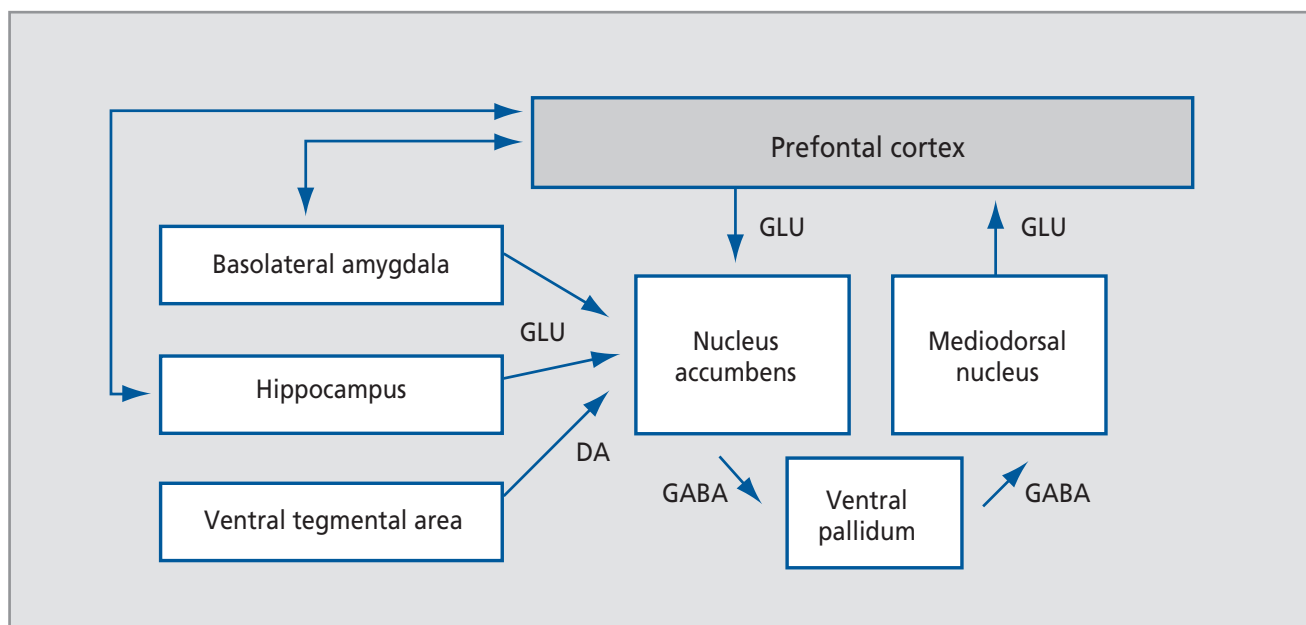
even sustained dopaminergic blockade in about 25% of patients with schizophrenia.<sup>69</sup>

In this context, it is also important to note a critical difference in the pro-psychotic effects of DA agonists, on the one hand, and NMDA antagonists or serotonin 5-HT<sub>2A</sub> agonists, on the other. In healthy individuals, drugs such as ketamine or lysergic acid diethylamide (LSD) induce a psychotic state immediately upon drug exposure, while sustained administration of DA agonists is required for the emergence of psychotic symptoms (for a review, see reference 95). This unique effect of DA agonists suggests that some plasticity or neuroadaptation is required between the hyperstimulation of D<sub>2</sub> receptors and the psychotic experience.

To account for these data, one must postulate that, with time, increased DA activity triggers neuroplastic adaptation “downstream” from the mesolimbic dopaminergic synapse and that, once established, these neuroplastic changes become independent of increased DA activity. Positive symptoms circuits might become “hard wired” in prefrontal-ventrostriatal-ventropallidal-mediodorsal-thalamoprefrontal loops<sup>67,96</sup> (Figure 3). Excessive DA stimulation maintains the potential to activate these neuronal ensembles (as demonstrated by the relationship between D<sub>2</sub> receptor stimulation and worsening of positive symptoms), but the evidence suggests that, at least in some patients, these symptoms might become independent of continuous DA stimulation (as demonstrated by the observation that some patients exhibit severe positive symptoms in the absence of detectable abnormalities in synaptic DA). Thus, the emergence of treatment-resistant positive symptoms suggests that these symptoms have taken on “a life of their own,” ie, have become independent of DA stimulation. A better understanding of the consequences of sustained dopaminergic activity on the plasticity of prefrontal-striatothalamic loops is needed to further characterize the neurobiological effects of sustained hyperdopaminergic state.

The ubiquitous role of DA in the creation of these hypothetical psychotic ensembles remains to be established. Whether DA hyperactivity has been present at some point or another in the life of every schizophrenic patient with positive symptoms is uncertain. A deficiency in glutamate transmission that would impair appropriate modulation of prefrontal-striatothalamic loops by afferents from the amygdala-hippocampal complex is another mechanism that might induce positive symptoms in the absence of overactivity of DA transmis-

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**Figure 3.** Schematic representation of ventral limbic circuits implicated in the positive symptoms of schizophrenia (adapted from reference 96). The nucleus accumbens receives major excitatory inputs from the prefrontal cortex (PFC), basolateral amygdala, and hippocampus, and dopamine (DA) input from the ventral tegmental area (VTA). The nucleus accumbens sends inputs to the mediodorsal nucleus of the thalamus. The mediodorsal nucleus provides excitatory inputs back to the PFC. The nucleus accumbens is a crucial node in this circuit, where inputs from the PFC are gated by excitatory projections from the hippocampus and the basolateral amygdala, and DA projections from the VTA. It is proposed that increased DA activity induces perturbation in the information flow within this circuit, in the modulation of this information by hippocampus and amygdala, and in the gating of sensory information by the thalamus. If sustained, the increase in DA activity might lead to neuroplastic changes in this circuit resulting in the emergence of a psychotic experience. GLU: glutamate; GABA:  $\gamma$ -aminobutyric acid.

sion.<sup>12,68,97</sup> In other words, endogenous sensitization of dopaminergic systems might represent only one avenue, among others, leading to chronic and/or recurrent psychotic episodes.

## Implications for treatment

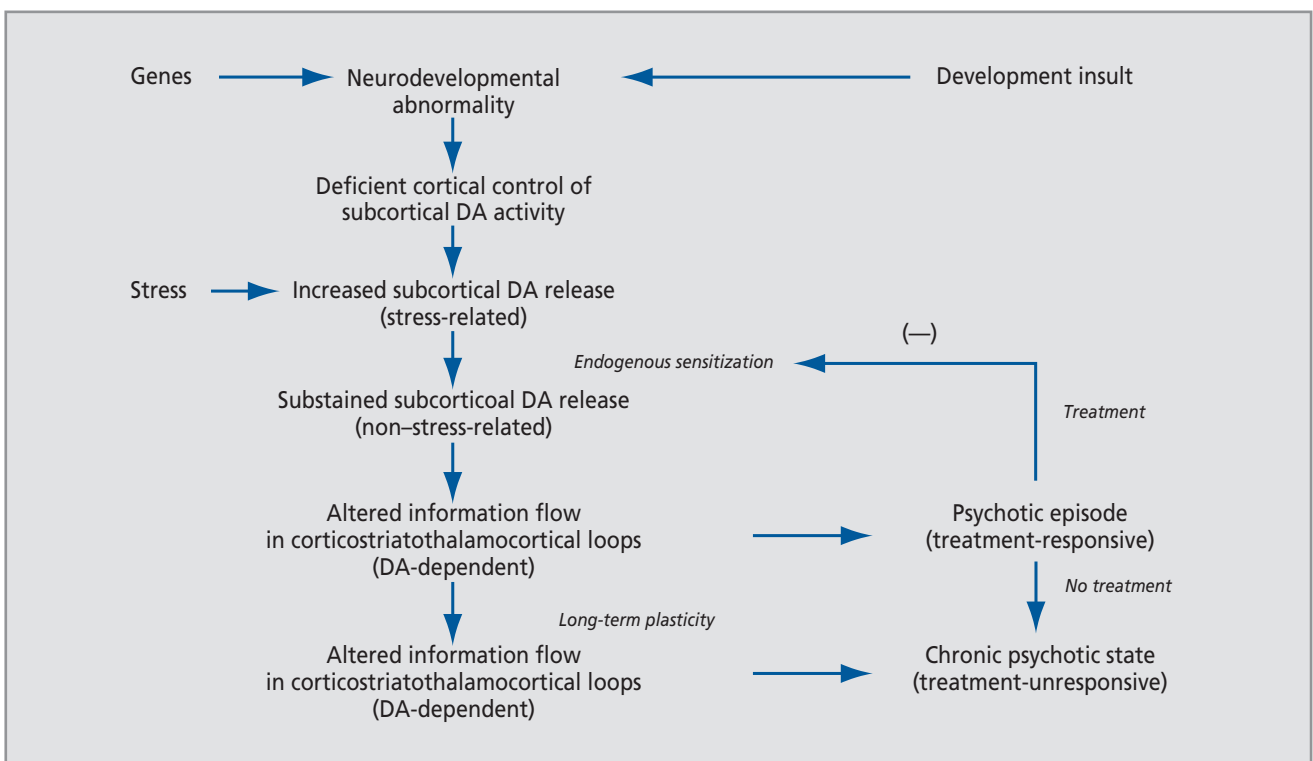
The model proposed here involves a three-step process, in which neurodevelopmental abnormalities associated with schizophrenia set the stage for sensitization of DA systems. Sustained hyperactivity of DA neurons resulting from this sensitization process leads to neuroplastic changes downstream from the DA synapse (Figure 4). This neuroplastic adaptation underlies the psychotic experience. If untreated, activities in these aberrant circuits become independent from increased DA activity. On the other hand, early treatment will reverse these neuroplastic changes and induce an extinction of the sensitization process. In other words, it might be important to evaluate the role of DA in schizophrenia within the context of a

brain with a history, divided into a predopaminergic, a dopaminergic, and a postdopaminergic era.

This model clearly supports the rationale for  $D_2$  blockade during periods of illness exacerbation, and the need for early intervention during prodromal states. It also suggests the need for new relapse prevention strategies. Currently, pharmacological “maintenance” during remission phases is based on dopaminergic  $D_2$  receptor blockade. These treatments succeed at preventing the reemergence of sensitization and at reducing the risk of relapse. Yet, they exert their preventive effect at the price of inducing a hypodopaminergic state, which is associated with significant adverse effects and a lower quality of life. A better understanding of the neurobiological mechanisms that trigger the reemergence of sensitization might lead to new relapse prevention strategies sparing  $D_2$  receptor function. In other words, the apparent normality of DA transmission during illness remission might be a more important finding of these studies than the dysregulation during illness exacerbation.

Moreover, this model calls for better understanding of the long-term consequences of exaggerated stimulation of  $D_2$  receptors on cortico-subcortical connectivity. The observation that, in some patients, psychotic symptoms are independent of DA transmission (these symptoms are experienced in the presence of apparently normal levels of synaptic DA and show little or no response to  $D_2$  receptor blockade) is another fundamental observation from these imaging studies. This observation supports the need for the development of new therapeutic approaches. Finally, it should be reemphasized that the presence of

positive symptoms is only one aspect of the symptomatology presented by these patients. While they might be the most visible expression of the illness, these symptoms are not the most enduring nor the ones associated with most disability, at least in the postneuroleptic era. Cognitive impairments appear to precede and outlive psychotic episodes, and their severity is one of the best predictors of poor outcome.<sup>6</sup> While the brain-imaging studies reported here supported the role of subcortical hyperdopaminergic activity in the pathophysiology of positive symptoms, the potential role of



**Figure 4.** Model describing the role of subcortical dopamine (DA) dysregulation in the chain of events leading to clinical expression of positive symptoms in schizophrenia. It is postulated that neurodevelopmental abnormalities, resulting from complex interactions of genetic vulnerability and pre- or perinatal insults, induce, among other consequences, impaired regulation of subcortical DA activity by the prefrontal cortex (Figure 2). The lack of normal buffering systems results in vulnerability of DA systems to develop a process of endogenous sensitization. Excessive DA activity, initially as a response to stress, initiates a positive feedback loop, in which elevated DA activity becomes self-sustained even in the absence of stressors or other salient stimuli. This excessive DA activity perturbs information flow in corticostriatalthalamocortical loops (Figure 3), which results over time in remodeling of these circuits. The hypothetical neuroplastic response to DA hyperactivity mediates alterations of information processing leading to a psychotic episode.  $D_2$  receptor blockade not only recalibrates DA responsivity by interrupting the endogenous DA process, but also reverses the neuroplastic changes that took place downstream from the DA synapse. However, in the absence of treatment, these neuroplastic changes become progressively "hard-wired," and activity in these reentrant psychotic ensembles becomes independent of sustained DA activity and unresponsive to  $D_2$  receptor blockade. While this model integrates observations from brain-imaging studies of DA synaptic activity in schizophrenia, its speculative nature must be emphasized. Furthermore, this does not imply that this chain of events is the only avenue leading to the emergence of psychotic symptoms in the schizophrenic brain. Nonetheless, it provides a number of testable hypotheses and directions for future research.

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prefrontal deficit in DA transmission in the pathophysiology of cognitive impairment remains to be firmly established. The development of new brain-imaging techniques enabling the study of prefrontal DA transmission is warranted to further explore this other face of the dopaminergic imbalance hypothesis of schizophrenia. □

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## **La dopamina en la historia del cerebro esquizofrénico: contribuciones recientes de los estudios de neuroimágenes**

*Los desarrollos recientes de las imágenes de la tomografía de emisión de positrones ("PET") y de la tomografía computerizada de emisión de fotones únicos ("SPECT") han permitido la medición de la transmisión dopaminérgica en los receptores D<sub>2</sub> del cerebro humano en vivo. Los estudios que han utilizado estas técnicas han demostrado que el aumento de la estimulación dopaminérgica de los receptores D<sub>2</sub> estriatales en la esquizofrenia está asociada con el primer episodio de la enfermedad y los episodios posteriores de exacerbación del cuadro. Aun cuando esta disregulación de la función dopaminérgica no está asociada con la severidad de los síntomas positivos per se, el aumento de la actividad dopaminérgica sináptica es predictora de una buena respuesta terapéutica al tratamiento antipsicótico. Durante los períodos de remisión de la enfermedad no se han detectado anomalías de la función dopaminérgica. Estos hallazgos están integrados en un modelo clínico que propone que en la esquizofrenia las anomalías del neurodesarrollo de las conexiones cortico-subcorticales se traducen en una vulnerabilidad del sistema dopaminérgico mesolímbico para el desarrollo de un proceso de sensibilización endógeno, y la consecuente hiperestimulación mantenida de los receptores D<sub>2</sub> induce cambios neuroplásticos dentro de los circuitos cortico-estriatales/ tálamo-corticales, que afectan los procesos de información y la experiencia psicótica subyacente.*

## **Dopamine et cerveau schizophrénique : contributions récentes des études d'imagerie cérébrale**

*Les progrès récents de la tomographie par émission de positron (TEM) et de la tomographie par émission de simple photon ont permis de réaliser des mesures fonctionnelles de la transmission de la dopamine (DA) au niveau des récepteurs D<sub>2</sub> dans le cerveau humain vivant. Les études utilisant ces techniques ont démontré qu'au cours de la schizophrénie tant l'épisode inaugural que les épisodes ultérieurs d'exacerbation de la maladie sont associés à une augmentation de la stimulation dopaminérgique des récepteurs D<sub>2</sub> striataux. Alors que ce trouble de la régulation de la fonction dopaminérgique n'est pas en soi associé à la sévérité des symptômes positifs, l'augmentation de l'activité synaptique de la DA est en revanche prédictive d'une réponse thérapeutique positive au traitement antipsychotique. En outre, aucun trouble de la fonction dopaminérgique n'est détecté au cours des périodes de rémission de la maladie. Un modèle clinique de la schizophrénie intégrant ces données est proposé selon lequel, d'une part, les anomalies neurodéveloppementales des connexions cortico-sous-corticales se traduiraient par une vulnérabilité du système mésolimbique dopaminérgique au développement d'un processus de sensibilisation endogène, et d'autre part, l'hyperstimulation prolongée résultante des récepteurs D<sub>2</sub> induirait des modifications neuroplastiques au sein des circuits cortico-striato-thalamo-corticaux, perturbant le traitement des informations et sous-tendant l'expérience psychotique.*



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