Do we still believe in the dopamine hypothesis? New data bring new evidence

Anissa Abi-Dargham
Department of Psychiatry, Columbia University, 1051 Riverside Drive, New York, NY 10032, USA

Abstract
Schizophrenia is characterized by positive symptoms, negative symptoms and cognitive impairment. The dopamine hypothesis of schizophrenia postulates that an excess of dopamine subcortically is associated with the positive symptoms. At the same time, the negative and cognitive symptoms of schizophrenia are thought to arise from a deficit of dopamine in the cortex. Evidence for the co-existence of subcortical dopamine excess and cortical dopamine deficit in the schizophrenic brain is presented. Neuroreceptor-imaging techniques, such as SPECT and PET, have been used to provide that evidence. After amphetamine challenge (to stimulate dopamine release), dopamine transmission was substantially increased in the brains of schizophrenic subjects compared with healthy controls. In addition, amphetamine challenge was associated with an increase in positive symptoms of schizophrenia. Furthermore, acute dopamine depletion studies indicated that there was an increased occupancy of D_2 receptors by dopamine at baseline in schizophrenia in comparison with healthy controls. This is consistent with the notion of hyperstimulation of D_2 receptors in schizophrenia. In the cortex, dopamine type-1 (D_1) receptors were found to be up-regulated in patients with schizophrenia compared to controls; in the dorsolateral prefrontal cortex, a brain region involved in working memory, this increase correlated with a poor performance on the n-back task. The up-regulation of D_1 receptors may represent a compensatory effect of the dopamine deficit in the cortex. These findings provide evidence for a cortical/subcortical imbalance in the schizophrenic brain.

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Introduction
Schizophrenia is characterized by positive, negative and cognitive symptoms, all of which are thought to arise from a dopaminergic imbalance in the brain. Positive symptoms may be related to excessive dopamine function, such as antipsychotic medications, which are effective at treating positive symptoms, all have common antidopaminergic properties. Negative symptoms and impairment in higher cognitive functions are thought to be related to a dysfunction of the dorsolateral prefrontal cortex (DLPFC) possibly from inappropriate stimulation of dopamine type-1 (D_1) receptors. In the last few years, neuroimaging techniques have been used to examine dopamine function in the schizophrenic brain and these studies are reviewed here. Evidence for the co-existence of subcortical dopamine excess and cortical dopamine deficit in the schizophrenic brain is presented.

A brief overview of neuroimaging techniques
The methodology of neuroreceptor imaging has been previously described in detail (Abi-Dargham, 2002). Briefly, neuroimaging techniques, such as SPECT (single photon emission computerized tomography) and PET (positron emission tomography), involve the injection of a radiotracer (a radioactively labelled drug or agent) into a subject that will concentrate in brain areas containing a specific neuroreceptor. For example, the distribution of D_2 receptors can be visualized using SPECT and the radiotracer [^123]IBZM (iodo-2-hydroxy-6-methoxy-N-[1-ethyl-2-pyrrolidinyl methyl] benzamide), an agent similar to amisulpride or sulpiride. Images of the whole brain are then acquired over time to construct a time–activity curve; simultaneously, blood samples are drawn for analysis.
of the input function, a measure of the amount of radiotracer that actually reaches the brain. From these two parameters, the binding potential can be derived. The binding potential is defined as the product of the density of the receptors and the affinity of the radiotracer, which correlates with the number of receptors in that brain region.

The dopamine hypothesis in schizophrenia

Dopaminergic pathways begin in the midbrain, in areas such as the ventral tegmental area (VTA) and the substantia nigra, and project to various regions of the brain; projections to the cortex and ventral striatum are called mesocortical dopaminergic projections and mesolimbic dopaminergic projections respectively. A deficit of dopamine in the cortex is thought to result in the hypostimulation of D₁ receptors, the predominant dopamine receptor subtype in this area, and consequently, negative and cognitive symptoms. Positive symptoms, on the other hand, arise from an excess of dopamine subcortically that causes the hyperstimulation of D₂ receptors.

The classical dopamine hypothesis of schizophrenia postulates that an excess of dopamine subcortically is associated with positive symptoms of schizophrenia. This belief was based on two observations: firstly, that sustained exposure to D₂ receptor agonists induces schizophrenia-like positive symptoms and secondly, that all drugs with proven antipsychotic effects block D₂ receptors to some degree. This is why D₂ receptor antagonists may be effective at relieving the positive symptoms of psychosis. About 10 years ago, the classical dopamine hypothesis of schizophrenia was reformulated to include a new nuance that accounted for the negative and cognitive symptoms of schizophrenia (Davis et al., 1991). Observations that cognitive impairment is associated with the prefrontal cortex (PFC) and that, in animals, induced dopamine depletion in the PFC produce cognitive impairment, lead to the proposal that a lack of dopamine cortically results in cognitive deficits. Thus, the revised dopamine hypothesis posits that a deficit of dopamine in the cortex and an excess of dopamine subcortically co-exist.

Dopamine in subcortical regions

Increased dopamine transmission in schizophrenia after challenge

Changes in synaptic dopamine levels were assessed using in-vivo binding techniques and competition between endogenous levels of dopamine and radiotracers for binding to D₂ receptors. Brain scans were performed before (to obtain baseline D₂ receptor availability) and after amphetamine challenge, which causes dopamine and other neurotransmitters to be released into the synapse. An increase in the concentration of endogenous dopamine results in a decrease in the amount of radiotracer able to bind to the D₂ receptor. The difference between the two brain scans reflects the amount of dopamine released after the amphetamine challenge.

Dopamine transmission in patients with schizophrenia has been investigated in many studies using the paradigm described above (Abi-Dargham et al., 1998; Breier et al., 1997; Laruelle et al., 1999). All studies showed similar results: after challenge with amphetamine, dopamine transmission was substantially increased in schizophrenic subjects compared with healthy controls. In the study by Laruelle et al. (1999), patients with schizophrenia displayed, on average, a 2.5-fold higher amphetamine-induced displacement of [¹²³I]IBZM than controls (17% vs. 7%; p = 0.005).

In patients with schizophrenia, the amphetamine challenge also induced an increase in positive symptoms (Figure 1; Laruelle et al., 1999). It is well established that patients with schizophrenia who take stimulants may aggravate their psychosis. After one single exposure to amphetamine, a patient with schizophrenia has a 40% chance of worsening their psychotic symptoms while a healthy control has a 0%
chance. This was the first evidence showing that a direct relationship existed between dopamine release and the genesis of psychosis.

**Increased baseline occupancy of D2 receptors by dopamine in schizophrenia**

The baseline occupancy of D2 receptors by dopamine was studied in patients with schizophrenia and healthy controls. SPECT scans were performed before (to assess D2 receptor availability at baseline) and during acute dopamine depletion, which was accomplished using α-methyl para-tyrosine (AMPT). AMPT blocks tyrosine hydroxylase preventing new dopamine synthesis; after a significant time, endogenous dopamine is depleted from the synapse, and a greater number of D2 receptors are available to the radiotracer. The difference between the two brain scans is indicative of the proportion of D2 receptors that is occupied by dopamine at baseline.

After 48 h of AMPT administration, D2 receptor availability had increased significantly from baseline in patients with schizophrenia compared to controls (19% vs. 9%; \( p = 0.005 \); Abi-Dargham et al., 2000). Furthermore, after 6 wk of antipsychotic treatment, subjects with higher synaptic levels of dopamine at baseline showed a significantly greater improvement of positive symptoms (\( r^2 = 0.45, p = 0.01 \); Figure 2). In contrast, subjects who experienced positive symptoms in the presence of apparently normal stimulation of D2 receptors by dopamine showed little improvement of these symptoms. These data supported the notion of hyperstimulation of D2 receptors in schizophrenia as one of the causes of psychotic symptoms.

**Dopamine in cortical regions**

**D2 receptor up-regulation in the DLPFC**

In schizophrenia, many abnormalities have been found to exist in the cortex (Lewis and Lieberman, 2000). As the D2 receptor subtype is the most prominent dopamine receptor subtype present in this area, D2 receptor availability was investigated in patients with schizophrenia and healthy controls (Abi-Dargham et al., 2002). Subjects were matched for age, gender, ethnicity, family socio-economic status, and for smoking, as smoking is known to affect the dopaminergic system. D2 receptors were shown to be increased throughout the cortex in schizophrenic patients compared to controls, but the only area to show a significant difference was the DLPFC (\( p = 0.02 \); Abi-Dargham et al., 2002).

**Assessment of working memory**

The DLPFC is crucial in working memory, that is, the ability to keep information on-line for short periods while an action is executed. Impairment of working memory is also a core feature in schizophrenia. To test working memory, the n-back task was used (Cohen et al., 1994): subjects were required to monitor a series of letters presented sequentially on a computer screen and to respond when a letter was identical to (i) the one that immediately preceded it (1-back), (ii) the one presented two letters back (2-back) or (iii) three letters back (3-back). The degree of difficulty increases in this task because people have to remember which letters they are seeing and update this information as they continue with the task.

Patients with schizophrenia performed less well on working-memory tests than controls (Abi-Dargham et al., 2002), a finding that is well established within the field. For all three tasks, patients performed significantly worse than controls (1-back, \( p = 0.011 \); 2-back, \( p = 0.005 \); 3-back, \( p = 0.015 \), and the difference appeared to increase as the task’s level of difficulty increased. Interestingly, a relationship was found to exist between the pathological increase in D3 receptors [as shown by DLPFC binding potential (BP)] and the performance on working memory: in patients with schizophrenia, high DLPFC receptor availability was associated with low adjusted hit rate (AHR) for the 2-back and 3-back task. The relationship between DLPFC \(^{11}C\)NNC 112 BP and AHR for the 3-back task is presented in Figure 3. This relationship was only present in patients with schizophrenia and not in controls.
Thus, cortical D<sub>1</sub> receptor up-regulation appears to be a strong predictor of poor performance on the n-back task in patients with schizophrenia. The up-regulation of D<sub>1</sub> receptors may represent a compensatory effect of the dopamine deficit in the cortex. However, this up-regulation is not functional and so working-memory performance remains deficient due to lack of stimulation by the endogenous transmitter, dopamine.

How can the subcortical dopamine excess and the cortical dopamine deficit co-exist at the same time?

Dopamine transmission is regulated by complex circuitry in the brain involving other neurotransmitters such as γ-aminobutyrate (GABA) and glutamate. In a previous study, dopamine release in controls was increased to the range seen in patients with schizophrenia after amphetamine challenge by pre-treatment with ketamine (Kegeles et al., 2000). Ketamine, an antagonist of NMDA receptors, a subtype of glutamate receptors, caused a higher level of amphetamine-induced dopamine release in patients with schizophrenia than controls. Thus, a disruption of glutamatergic neuronal systems results in alterations in dopaminergic transmission.

Dopamine neurons in the VTA are under the control of an excitatory system, of glutamatergic cells projecting from the cortex, and a brake system, mediated by GABAergic cells (Figure 4). If the coordination of the activation and brake system is deficient for any reason, such as the presence of abnormalities in the glutamatergic pyramidal cells or in NMDA hypofunction, as postulated in schizophrenia, dopamine transmission subcortically can be affected. If both systems are deficient the effect of the brake system is speculated to have the greatest effect on subcortical dopamine. In normal subjects, these two systems would tend to cancel each other out; however, in schizophrenia, under conditions that cause an excess of dopamine to be released, such as stress or amphetamine challenge, there would be insufficient brake to

Figure 3. Relationship between [11C]NNC 112 BP (binding potential) in the DLPFC and performance (AHR) at the 3-back task in (a) healthy controls (r² = 0.02, p = 0.64) and (b) patients with schizophrenia (r² = 0.46, p = 0.004). (Adapted from Abi-Dargham et al., 2002.)

Figure 4. Diagrammatical representation of the activation and brake systems that regulate dopamine transmission. GLU, glutamatergic neurons; GABA, GABAergic neurons; VST, ventral striatum; VTA, ventral tegmental area; MC DA, mesocortical dopaminergic projection; ML DA, mesolimbic dopaminergic projection; PPT, pedunculopontine tegmentum.
reduce the levels of dopamine. At the same time, stimulation on the mesocortical dopaminergic projections would be inadequate, so low dopamine levels may occur in the cortex. Low dopamine levels will lead to suboptimal stimulation of the D\textsubscript{1} receptor and a deficit in working-memory performance, which has been shown by Goldman-Rakic et al. (2000) to be critically dependent on D\textsubscript{1} activation. In addition, these alterations feed into each other as it has been shown that cortical dopamine has an inhibitory effect on subcortical dopamine, by the seminal work of Pycock et al. (1980). This deficit in cortical dopamine may itself contribute to excess in subcortical dopamine. Therefore, an abnormality in the circuitry regulating dopamine and involving these other neurotransmitters would result in what has been observed—an excess of dopamine subcortically and presumably a deficit of dopamine cortically.

Conclusions

Neuroimaging studies have contributed to a better understanding of the pathophysiology of schizophrenia. In particular, imaging dopamine transmission through endogenous competition and depletion paradigms have shown strong evidence for excess subcortical dopamine related to positive symptoms and to the response of these symptoms to antipsychotics. In the cortex, there is emergent evidence for a deficit in dopamine related to up-regulation of the D\textsubscript{1} receptor in that brain region and cognitive dysfunction. These abnormalities may both be a downstream effect of alterations in prefrontal connectivity involving other neurotransmitters such as GABA or glutamate. More research is needed to address these interactions.

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