The Revised Dopamine Hypothesis of Schizophrenia: Evidence from Pharmacological MRI Studies with Atypical Antipsychotic Medication

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ABSTRACT ~ The revised dopamine (DA) hypothesis states that clinical symptoms of schizophrenia are caused by an imbalance of the DA system. In this article, we aim to review evidence for this hypothesis by evaluating functional magnetic resonance imaging studies in schizophrenia. Because atypical drugs are thought to have a normalizing effect on DA neurotransmission, we have focused on pharmacological MRI (PhMRI) studies that explore the effect of these drugs on prefrontal and striatal brain activity in schizophrenia patients. We encountered a total of 13 studies, most of which reported enhanced prefrontal activity associated with alleviation of negative symptoms and improvement of cognitive functions, following treatment with atypical antipsychotics. Besides increasing prefrontal cortex activity, atypical antipsychotics have also shown to be effective in the regulation of striatal functioning. The current PhMRI findings support the revised DA hypothesis of schizophrenia by confirming hypoactivity of the prefrontal cortex in schizophrenia and, following atypical antipsychotics, improvement of prefrontal and subcortical functions reflecting enhanced DA activity. Psychopharmacology Bulletin. 2008;41(1):121-132.

INTRODUCTION

The majority of in vivo dopamine (DA) studies of schizophrenia have been performed with positron emission tomography (PET) and single-photon emission computed tomography (SPECT). The use of these techniques has allowed the quantification of DA transmission in schizophrenia, mainly by measuring the availability of D2 receptors,1,2 and more recently by measuring D1 receptor availability.3,4 In contrast to PET and SPECT, functional magnetic resonance imaging (fMRI) is not suitable for direct visualization of changes in DA-receptor
density; nevertheless, this method allows for measuring changes in human brain activity in the absence of radiation exposure and with a higher temporal and spatial resolution than SPECT or PET. Because fMRI measures hemodynamic changes induced by local alterations in neuronal activity, fMRI investigations coupled with DA manipulation can provide information on the physiological effects of DA beyond its primary site of action.6–8 This innovative approach in imaging, pharmacological MRI (PhMRI), can be used for assessments of cognitive and emotional functions during pharmacological manipulation that are not possible with PET or SPECT. PhMRI is therefore a promising tool for investigating the hypothesized imbalance of the DA system in schizophrenia.

The discovery of antipsychotic drugs for the treatment of schizophrenia in 1952 provided a first indication for the involvement of DA in this disorder. The original DA hypothesis of schizophrenia assumed that the positive symptoms (hallucinations, delusions, thought disorganization) of this disease were being caused by increased DA neurotransmission. Neuroleptics were shown to have the capacity to increase the turnover of DA,2–11 next to the effectiveness to block DA D₂ receptors mainly in the subcortical regions.12–15 However, given the shortcomings of the conventional antipsychotic medication to treat negative symptoms (anhedonia, withdrawal, lack of motivation) and cognitive deficits in schizophrenia, the mechanisms of actions of antipsychotics and the role of the DA system required further investigation. In animal studies, hyperactivity of subcortical DA neurons was found to be related to hypoactivity of frontal cortical DA neurons.15,16 Therefore, the original DA hypothesis was revised, and it was suggested that positive symptoms could be associated with excessive DA transmission in subcortical regions, whereas negative symptoms could be related to a concomitant deficit in cortical DA transmission.17,18 Earlier fMRI investigations, without pharmacologic challenge, have found some evidence for the concept of frontal hypoactivity, by showing reduced activation during prefrontal cognitive tasks (working memory, attention, and executive functions) in the ventrolateral prefrontal cortex (VLPFC), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate in nonmedicated or medication-naïve patients, relative to healthy controls.19–21

How can we review further evidence for the revised DA hypothesis of schizophrenia? In contrast to the robust D₂ blocking effect of typical antipsychotics,22 most of the atypical neuroleptics have been shown to induce a moderately selective, short-lasting and low level of subcortical mesolimbic DA D₂ receptor blockade.23–25 In addition, in animal models, these drugs appear to enhance prefrontal DA activity.26 If atypical antipsychotics are found to be more effective in improving cognitive functions and reducing negative symptoms, then this will provide
additional support to the revised DA hypothesis of schizophrenia because of atypical enhancement of frontal activity and mild blockade of subcortical D₂. In order to present additional evidence for the revised DA hypothesis of schizophrenia, we review frontal and subcortical imaging studies that combine PhMRI and DA manipulation with atypical antipsychotic drugs in schizophrenic patients (see Table 1).

Frontal Brain Activity

The first PhMRI study to evaluate the differential effects of typical and atypical neuroleptics on frontal brain activation in schizophrenic patients was conducted by Honey et al. This study compared patients with chronic schizophrenia who continued on typical antipsychotics to patients that had been switched from a typical to an atypical antipsychotic, i.e., risperidone. Following 6 weeks of treatment, patients on risperidone showed enhanced activity in right DLPFC during performance of a working memory task. Although not statistically significant, Honey and colleagues also observed a trend toward improvement on symptomatic and cognitive scales in patients treated with risperidone. Next, a case study conducted by Lund et al. was able to show improvements on a working memory task as well as clinical improvement following treatment with the atypical drug olanzapine. In this case study, a young, antipsychotic-naïve schizophrenic man and his nonmedicated schizophrenic mother demonstrated enhanced frontal lobe activation during fMRI, after treatment with olanzapine. Comparable fMRI activations were seen after treatment with olanzapine in 12 healthy subjects.

Jones et al. compared fMRI activity between healthy controls and quetiapine-treated patients in a cross-sectional design. Patients had to perform a verbal fluency task as a measure of executive function. Both quetiapine-treated patients and healthy controls showed significantly increased activation in the left inferior frontal cortex compared to the drug-naïve group. Another study evaluated the effects of quetiapine on working memory and brain activation patterns in schizophrenia following 12 weeks of treatment. At baseline, patients with schizophrenia showed hypoactivation in right DLPFC and VLPFC compared to healthy controls. After treatment, increased activity in VLPFC and significant clinical improvement was observed, but no improvement of cognitive performance.

The short-term effects of atypical antipsychotic medication on the DLPFC and anterior cingulate cortex functioning were the focus of a study conducted by Snitz et al. A working memory task was designed to functionally dissociate the two regions, in a group of never-medicated first-episode schizophrenia patients. After 4 weeks of treatment with atypical antipsychotic, increased anterior cingulate cortex activity was
# Imaging Studies of Functional Pharmacology MRI in Schizophrenic Patients

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<td>8 Olanzapine 2 (8 m/2 f)</td>
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<td>Schnit et al.¹⁴</td>
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<td>MN = 23 (16 m/7 f), HC = 24 (13 m)</td>
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<td>Meiszenzahl et al.¹⁵</td>
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<td>Wolf et al.¹⁶</td>
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<tr>
<td>Juckel et al.¹⁷</td>
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<td>10 (6 m)</td>
<td>Various</td>
<td>13 (8 m)</td>
<td>HC = 10 (8 m/2 f)</td>
<td>Monetary reward task</td>
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PFC, prefrontal cortex; STR, striatum; Treat, treatment; Symp, symptom; Cogn, cognition; DF, drug-free; NM, never medicated; HC, healthy controls; m, male; f, female; B, baseline; WM, working memory; Neg, negative; Clo, Clozapine; Ola, Olanzapine; Que, Quetiapine; Hal, Haloperidol; Risperidone; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; LPFC, lateral prefrontal cortex; Ant. Cing, anterior cingulate; Temp, temporal; VSTR, ventral striatum; PANSS, positive and negative symptom scale; ↑, improvement; ↓, worsening.

found, but no changes in the DLPFC. These findings suggest that anterior cingulate cortex functioning may be especially sensitive to atypical antipsychotic treatment. Wolf et al.32 evaluated the effects of various atypical neuroleptics combined with multimodal psychiatric treatment (i.e., occupational therapy, physical exercise, supportive, psychotherapy and a psychoeducational intervention). In patients with schizophrenia, frontotemporal activity was bilaterally enhanced after 7–8 weeks treatment. These changes were associated with improved accuracy in a variety of cognitive domains and with reduction of psychopathology.

Genetic variations in prefrontal DA catabolism have been suggested to influence prefrontal brain function in schizophrenia.33,34 One fMRI study has investigated the effect of atypical medication olanzapine on prefrontal brain activation, by accounting for variations in a functional polymorphism (Val158Met) in the COMT gene. Following 8 weeks of treatment, individuals carrying a Met allele showed a greater increase in prefrontal activity, working memory performance, and a greater reduction in negative symptoms.35

In contrast with the earlier-cited studies, two other fMRI studies failed to show increased frontal activity after treatment with atypical antipsychotics. First, Ramsey et al.36 investigated the impact of atypical antipsychotic medication on brain activity patterns while controlling for performance differences in executive function. After correction for differences in performance, medication-naïve patients with schizophrenia showed a significant elevation of overall brain activity compared to healthy controls during an executive function task, while brain activity in medicated patients (olanzapine and clozapine) was similar to healthy controls. The authors suggested that schizophrenia may be associated with excessive, and thus ineffective, recruitment of frontal brain circuitry during logical reasoning. They proposed that atypical antipsychotics may reduce this neural inefficiency. Next, Schlösser et al.37 examined the effect of typical or atypical antipsychotic treatment on brain efficiency in schizophrenic patients compared to healthy controls. Their study combined fMRI with structural equation modeling analyses. Both typical or atypical drug treatment was associated with diminished parietofrontal connections in the left hemisphere. In addition, poor brain activation from the right VLPFC to DLPFC connectivity was found in the atypical treatment group, suggesting a negative effect of atypical drugs on neural prefrontal communication.

Apart from its influence on cognitive function, prefrontal DA transmission is also involved in emotion processing. Two studies have specifically investigated the effects of antipsychotics on negative symptoms and regional cerebral activity. Stip et al.38 measured brain activation in
12 schizophrenia patients, with flattened effect during passive viewing of sad film excerpts before and after treatment with quetiapine. Subsequent to the atypical antipsychotic treatment, there was an increase in prefrontal brain activity and alleviation of negative symptoms, as measured with the PANSS. Fahim et al. evaluated brain activity changes in schizophrenia patients during presentation of emotionally negative pictures. A 22-week treatment with quetiapine resulted in significant clinical improvement and increased prefrontal cortex activation particularly in the right DLPFC and the right anterior cingulate cortex, along with subcortical activation of the left putamen and the right amygdala.

In agreement with the revised DA hypothesis of schizophrenia, nine studies have confirmed enhanced prefrontal activity after treatment with atypical antipsychotics. In addition, improved prefrontal functioning was often associated with amelioration of negative symptoms and cognitive functions.

**Subcortical Brain Activity**

We have found two studies that have attempted to answer the question whether atypical antipsychotics might be more effective in treating negative symptoms than classic antipsychotics, because of differences in subcortical D2-blockade. First, the previously mentioned study by Fahim et al. suggests increased subcortical activity of the left putamen and improvement of negative symptoms after treatment with quetiapine.

Since negative symptoms may be associated with dysfunction of the brain reward system in schizophrenia, Juckel et al. used a monetary reward paradigm to measure ventral striatal activation in nonmedicated schizophrenic males and healthy controls. Healthy volunteers displayed significant activation in bilateral ventral striatum during reward anticipation, whereas drug-free schizophrenic patients showed reduced ventral striatal activation, and this was associated with the severity of negative symptoms. This finding seems to be at odds with the DA hypothesis and with the results of other studies, where increased, rather than decreased striatal D2 activity has been found in medication-free schizophrenics. However, Juckel et al. explained their results by suggesting that a high baseline striatal DA turnover in schizophrenics may increase the “noise” in the reward system, thus interfering with the neuronal processing of reward-predicting cues by phasic DA release. In agreement with this observation, amphetamine-induced DA release blunted ventral striatal activation elicited by reward-indicating cues in healthy control subjects. In a follow-up study by Juckel et al., patients were treated with either typical or atypical antipsychotics. Patients on atypical antipsychotics displayed ventral striatal activation in response
to reward similar to healthy controls. In contrast, patients treated with typical antipsychotics demonstrated no ventral striatal activation and reduced activation in left ventral striatum. Moreover, activity in the brain reward system was inversely correlated with the severity of negative symptoms.

**DISCUSSION**

The aim of the present article was to review the evidence from fMRI studies for the revised DA hypothesis of schizophrenia. We have focused on fMRI studies following DA challenge with antipsychotic medication in patients with schizophrenia. We have encountered a total of 13 studies, three of which dealt with the effect of atypical versus typical antipsychotic treatment. The majority of the studies have evaluated changes in cerebral activity related to cognitive performance and symptom improvement before and after several weeks of treatment with atypical antipsychotics. These PhMRI studies support the revised DA hypothesis by confirming the presence of decreased PFC activity in schizophrenia, as well as enhanced DA activity coupled with improvement of PFC functions following atypical antipsychotic treatment. In addition, increased striatal activation and improvement of negative symptoms was found after treatment with atypical antipsychotics, but not for typical antipsychotics.

**Limitations and Methodological Considerations**

A basic tenet of PhMRI is that modulatory effects on brain regions activated in response to either a sensory, motor, or cognitive input reflect drug action. However, it can be questioned whether enhanced prefrontal or striatal fMRI activity following antipsychotic drug therapy in fact represents enhanced DA activity. Beyond DA systems, it has been suggested that atypical drugs modulate frontal neuronal activity through an interaction between DA and other neurotransmitters. For instance, serotonin has an inhibitory effect on presynaptic DA release. In animals, serotonin 5HT2 blockade increased DA in cortical areas. Most of the atypical antipsychotics have 5HT2 antagonistic properties and may block excitatory actions of serotonin on inhibitory GABAergic interneurons. Consequently, serotonin 5HT2 antagonism may cause prefrontal activation through GABAergic interneurons. Hence, both DA and concomitant 5HT2 effects of atypical antipsychotics may result in enhanced functional activation of prefrontal cortex.

A methodological concern about fMRI studies featuring DA manipulation is that cerebral vasoregulatory effects of DA drugs may affect BOLD signal. Changes in BOLD-signal strength or shape may result from pharmacological effects on the hemodynamic response of the brain.
cortical vasculature instead of pharmacological effects on neuronal activity. However, the vasoconstrictive actions of DA drugs on cerebral blood flow do not necessarily affect the amplitude of the acute hemodynamic response to experimental stimulation.\(^5\) Besides, the suggested vasoconstrictive effects of DA drugs are at odds with the findings of increased cerebral blood flow in most of the studies we have found.

Another issue to be considered is the experimental design, i.e., the characteristics of cognitive and emotional paradigms during functional imaging studies, which are fundamental for the interpretation of the imaging results. Likewise, the performance accuracy of patients is likely to play an important role in the outcome of the imaging analyses.

The studies reporting hypofrontality, even after atypical antipsychotic treatment, appear to be limited by several methodological issues such as task complexity and failure to account for performance differences, both between groups and within groups,\(^32,33,52-54\) for example, by the use of blocked designs.\(^30,37\) For instance, the equation modeling analyses that Schlösser et al.\(^37\) conducted to examine changes in effective connectivity showed worsening of task performance and decreased neuronal activation in patients on either typical or atypical drugs. To explain these results, Schlösser et al. proposed that their data analyses were group-based and did not take into account the possible variations of cortical activation patterns in schizophrenic patients. Moreover, the findings by Ramsey et al.\(^36\) indicate that atypical antipsychotics stabilized excessive and ineffective recruitment of brain systems during logical reasoning, only after controlling for differences in performance.

Finally, it should be noted that although the main focus of PhMRI investigations in schizophrenia patients has been on the effects of atypical antipsychotics, most studies have adopted a longitudinal design (i.e., pre-post comparisons). As discussed earlier, this approach has been successful in demonstrating increased prefrontal activity as well as improved cognitive performance after atypical antipsychotic drug treatment in medication-naïve patients or nonmedicated patients. Few studies, however, have included patients on typical antipsychotics. A comparison group to evaluate typical vs. atypical antipsychotics would be a more appropriate procedure for investigating the revised DA hypothesis of schizophrenia.

**Other Lines of Evidence in Favor of the Revised DA Hypothesis**

In agreement with the PhMRI studies in the present review, results from PET studies have revealed a relationship between altered availability of cortical D\(_1\) receptor and cognitive function or severity of negative symptoms in schizophrenia,\(^3,5\) although increased as well as decreased D\(_1\) receptor availability has been found. These inconsistencies were also observed in a number of postmortem studies: cortical D\(_1\) receptor level
has been found to be unchanged in schizophrenic brains, but in others, a relative reduction of D₁ or a reduction of DA innervations was found. Postmortem investigations in medication-naive patients or nonmedicated patients may yield different results, since the administration of antipsychotics, alone or combined with other medication, is likely to induce neuronal adaptations within the DA system.

Further evidence in favor of the revised DA hypothesis has been provided by studies of DA agonists (like amphetamines or pergolide) in healthy subjects, which have suggested similar increase in prefrontal activity and in cognitive performance. In contrast, lowered subcortical striatal activity and decreased cognitive function have been found in healthy subjects after administration of typical D₂ blocking antipsychotics. In schizophrenia, DA-enhancing drugs like amphetamines or apomorphine have also been reported to ameliorate negative symptoms and cognitive deficiency, which was related to enhancement of prefrontal activity. Conversely, DA depletion with α-methyl-paratyrosine was found to result in decreased striatal DA activity, and to induce negative dysphoric symptoms in nonmedicated schizophrenia patients and in one healthy individual.

A final issue to consider is the role of individual genetic variation in the pathophysiology of diseases involving the DA neurotransmitter system. A well-known example is the functional polymorphism (Val158Met) in the COMT gene, which has been shown to modulate the effect of DA challenge. In healthy subjects, amphetamine was found to improve PFC efficiency in subjects with the high enzyme activity variant Val/Val of the COMT gene. Val homozygous subjects probably have relatively low levels of prefrontal synaptic DA, at baseline as well as with increasing cognitive demands. In contrast, Met allele carriers (the low activity enzyme) are characterized by higher prefrontal activity at baseline. In these subjects, however, amphetamine had no effect on cortical efficiency at low-to-moderate working memory load and even proved to be deleterious at a high working memory load. These results are in line with Bertolino’s finding that COMT-mediated variation in prefrontal DA turnover impacts the therapeutic profile of olanzapine.

**CONCLUSION**

The current hypothesis of DA in schizophrenia is that this disorder is associated with decreased DA activity in the prefrontal cortex, together with DA hyperactivity in subcortical areas. In the present review we focused on PhMRI studies that investigate the effect of atypical antipsychotics on brain activity in schizophrenia patients. Although PhMRI is not suitable for direct measurements of neurotransmitter status, this technique can be used to explore cognitive and emotional...
brain functioning during pharmacological manipulation. In addition, PhMRI has several other advantages, including superior temporal and spatial resolution, and absence of radiation exposure. Hence, PhMRI may rival PET/SPECT as a tool for investigating the DA imbalance in schizophrenia, particularly in longitudinal designs.

In agreement with the revised DA hypothesis, the PhMRI studies presented here have confirmed decreased activity in prefrontal cortex in schizophrenia and demonstrated improved function of prefrontal cortex and striatum, following DA modulation with atypical antipsychotics. In addition, atypical antipsychotics improved cognition and negative symptoms of schizophrenia, reflecting enhancement of DA activity. DA is certainly one of the main neurotransmitters involved in the pathophysiology of schizophrenia. Nevertheless, genetic variations and interactions with other neurotransmitters are critical factors involved in the etiology of this disease. Further studies are necessary to clarify these interactions and the action of atypical drugs on the various neuronal receptors.

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