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

By Fabiana da Silva Alves, MS, Martijn Figee, MD, Therese van Amelsvoort, MD, PhD, Dick Veltman, MD, PhD, and Lieuwe de Haan, MD, PhD

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.³⁻⁵ In contrast to PET and SPECT, functional magnetic resonance imaging (fMRI) is not suitable for direct visualization of changes in DA-receptor

Ms. da Silva Alves, Dr. Figee, Dr. van Amelsvoort, Dr. Veltman, and Dr. de Haan are affiliated with the Department of Psychiatry, Academic Medical Center, University of Amsterdam, Meibergdreef 5, 1070 AW, Amsterdam, The Netherlands.

To whom correspondence should be addressed: F. da Silva Alves, MS, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Postbox 75867, 1070 AW Amsterdam, The Netherlands; Tel: +31 (0) 20-8913609; Fax: +31 (0) 20-8913702; E-mail: f.dasilvaalves@amc.uva.nl

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,⁹⁻¹¹ next to the effectiveness to block DA D₂ receptors mainly in the subcortical regions.¹²⁻¹⁴ 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).

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