The influence of antipsychotic drug treatment on striatal dopamine D_2 receptors in patients remitted after a first episode of psychosis
A [11C]raclopride PET Study.

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Introduction

Antipsychotic drugs (APDs), all of which block the dopamine D_2 receptor, are the first line of treatment for patients who experience a first psychotic episode (FEP). Treatment discontinuation leads to higher rates of relapse, even in patients who have remitted from a psychotic episode[1].

Mechanism: long-term use of APDs can cause upregulation of the dopamine D_2 receptors[2].
Consequence: may make some patients more prone to future relapse than would be the case in the natural course of the illness without pharmacotherapy[3]. Thus, discontinuation of antipsychotic medication may provoke a psychotic episode that may be distinct from the underlying illness.

Aim: to determine whether increased dopamine D_2 receptor binding occurs in FEP patients after (long-term) antipsychotic treatment.

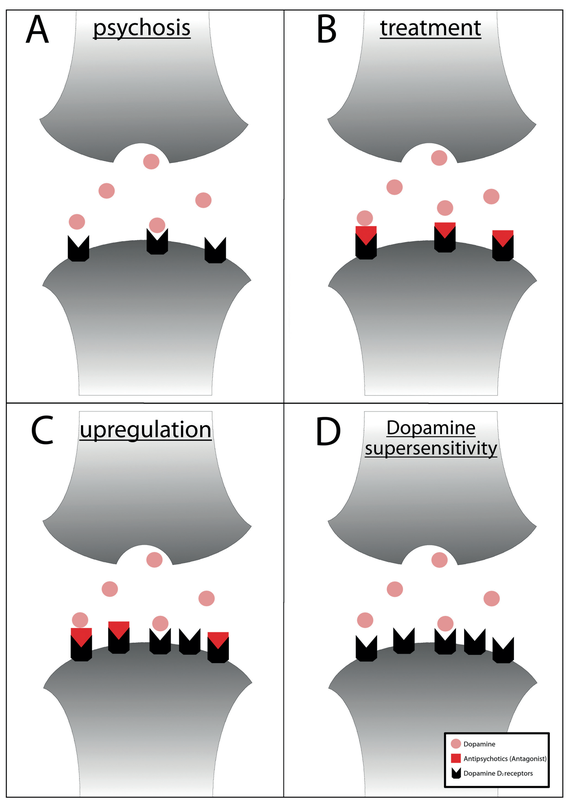


Figure 1:
A) Dopamine hypothesis states that the psychotic symptoms are related to heightened dopamine levels in the brain.
B) APDs (antagonists) block dopamine D_2 receptors and thereby reduce postsynaptic transmission.
C) Prolonged occupation of the receptors by antagonists leads to an increase in the number of dopamine D_2 receptors.
D) Dopamine function after exposure to APDs, increased postsynaptic transmission due to supersensitivity to action of dopamine.

Methods

A total of 30 male patients with a FEP in remission will undergo a positron emission tomography (PET) scan with the radioligand [11C]raclopride (see box 1).

Group 1
15 patients who discontinue medication after 3-6 months of remission

Group 2
15 patients who have used antipsychotic medication for at least 1 year and discontinue medication

The patients will undergo two PET scans:

1-7 days after discontinuation — 6-8 weeks after discontinuation

Objectives

Objective 1: to determine whether increased dopamine D_2 receptor binding occurs in FEP patients after treatment with APDs for *3-6 months*, compared to healthy individuals.

Objective 2: to compare dopamine D_2 receptor binding between FEP patients who have used APDs for *at least 1 year* (following current guidelines), with patients who have used APDs for *3-6 months*.

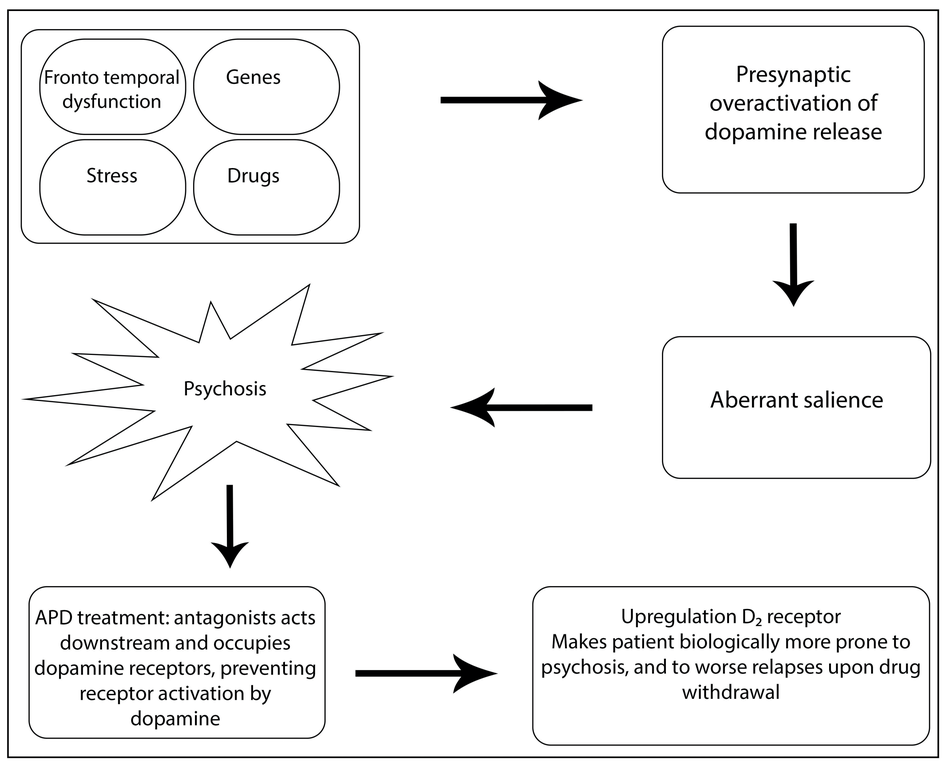


Figure 2: Adjusted from Howes & Kapur (2009). The dopamine hypothesis - version III - The final common pathway. Dopamine D_2 receptors are targeted by APDs, which can lead to upregulation of dopamine receptors.

Statistical analysis

Main study parameter: binding potential of [11C]raclopride in the striatum (caudate/putamen) determined using pharmacokinetic modelling (see Box 1).

The average and standard deviation of the [11C]raclopride BPND will be calculated for the study groups.

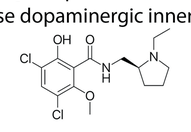
Analysis of variance (ANOVA) will be used to test for differences in the [11C]raclopride BPND between groups.
Multivariate analysis of variance (MANOVA) will be used to test for differences between patients and controls with group as the between-subjects factor and age as covariate.

Box 1: [11C]raclopride

The radioligand [11C]raclopride is a synthetic compound that acts as a selective antagonist on D_2 dopamine receptors, and thus can determine D_2 receptor binding.

The main study parameter is the binding potential of [11C]raclopride in the striatum (caudate and putamen), as this is a region receiving dense dopaminergic innervation.

The cerebellum will be used as a reference region.



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References
[1] Masand et al. (2009). Journal of Clinical Psychiatry.
[2] Chouinard, G. (1991). Schizophrenia research.
[3] Murray et al. (2016). The British Journal of Psychiatry.

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