Frontal cortex dopamine mechanisms in a rodent model of cognition

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Purpose

To evaluate the contributions of selective dopaminergic receptor ligands in a rodent model of cognitive deficits associated with schizophrenia.

Background

Currently treatments for schizophrenia have shown effectiveness in treating some, but not all, of the core deficits associated with the disease with the improvement of cognitive dysfunction being a unmet need.

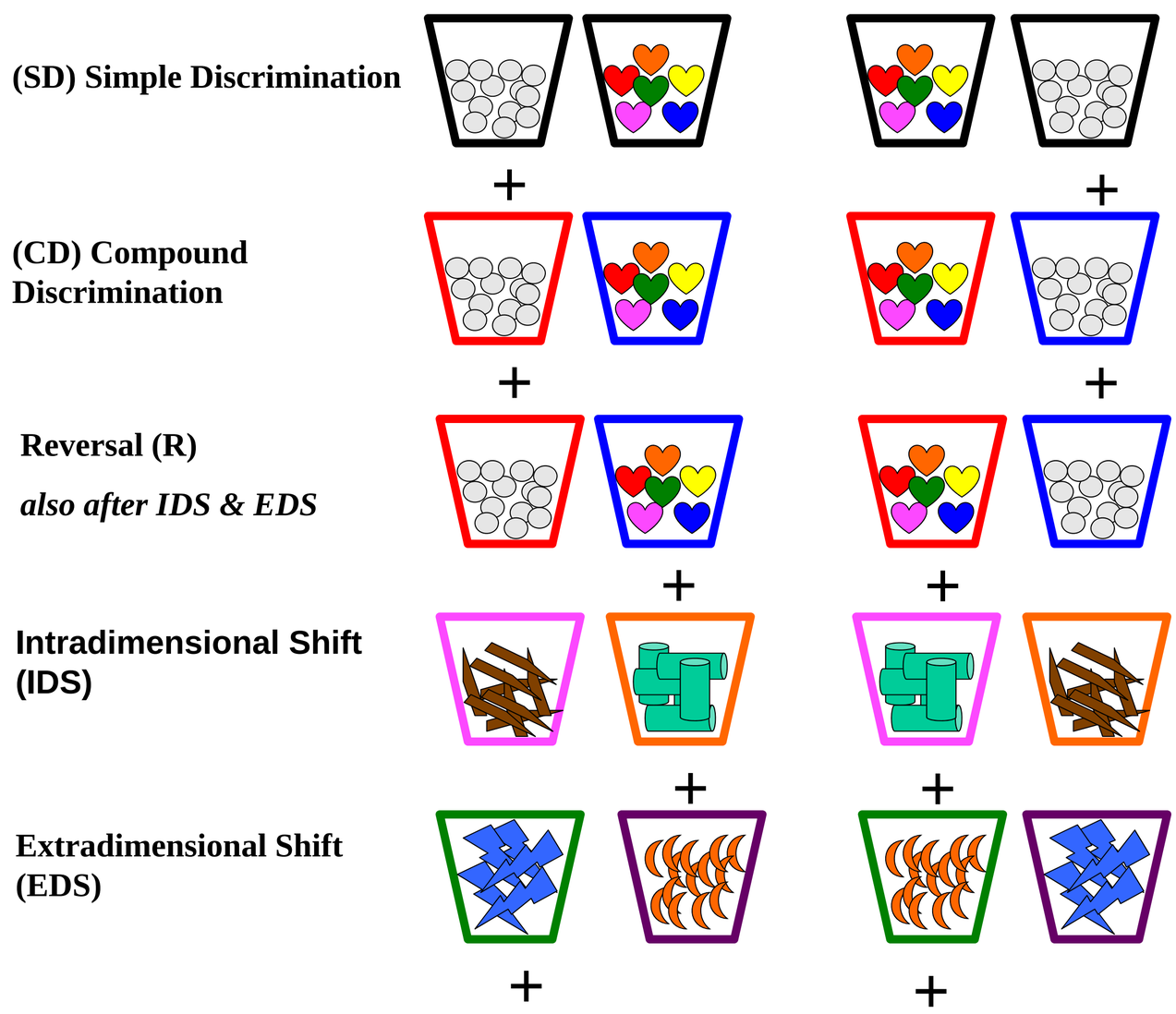
Cognitive improvement by pharmacological intervention is often difficult to demonstrate in healthy animals and may have little predictive validity for efficacy in disease models of schizophrenia. A more desirable starting point methodologically is one where normal cognition is disrupted and the effect of treatments in ameliorating deficits can be observed.

In the current experiments we utilized a rodent model of executive function that is sensitive to the effects of lesions, natural aging, and drug manipulations.

In addition, we employed a well-validated subchronic phencyclidine (PCP) administration treatment paradigm to produce enduring cognitive deficits similar to those observed in schizophrenia.

Given the well-documented involvement of dopamine in working memory and aspects of schizophrenia, we investigated the acute administration of different dopamine receptor agonists and antagonists on cognitive performance in the set-shifting task.

Methods: Attentional Set-Shifting schematic



Subjects: Adult male Long Evans rats (n=8-12/group)

Deficit production: Subchronic PCP treatment (5 mg/kg, BID, for 7 d) followed by washout prior to training.

Training & Testing: Animals were first trained to dig for food in pots and then successfully completed one odor and one media discrimination before the test session.

Treatment: Acute treatment with selective dopamine compounds

Results

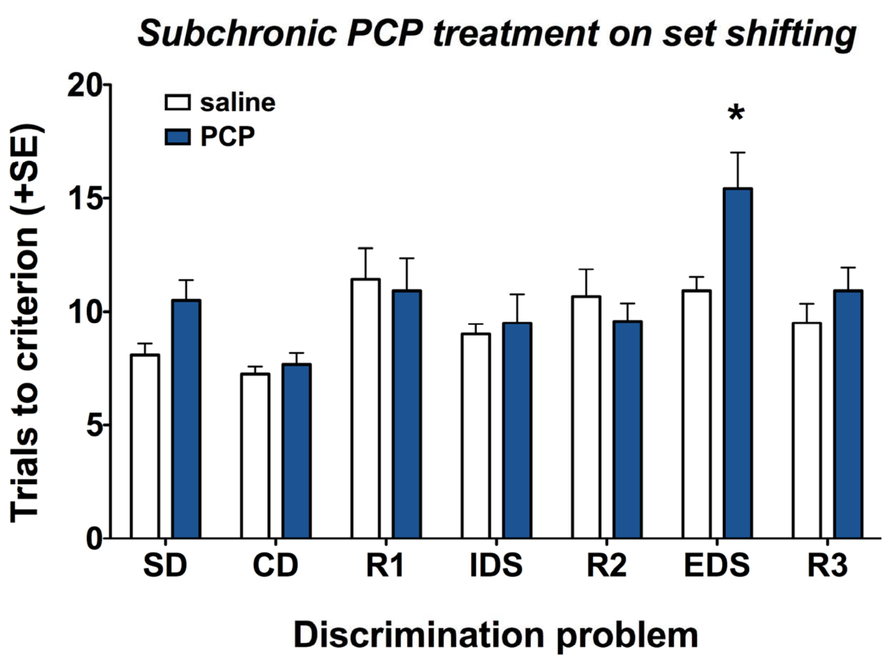


Figure 1. Subchronic PCP administration produces a selective impairment only at EDS; also the EDS problem is more difficult than IDS in saline anaimals, suggesting a cognitive set was formed

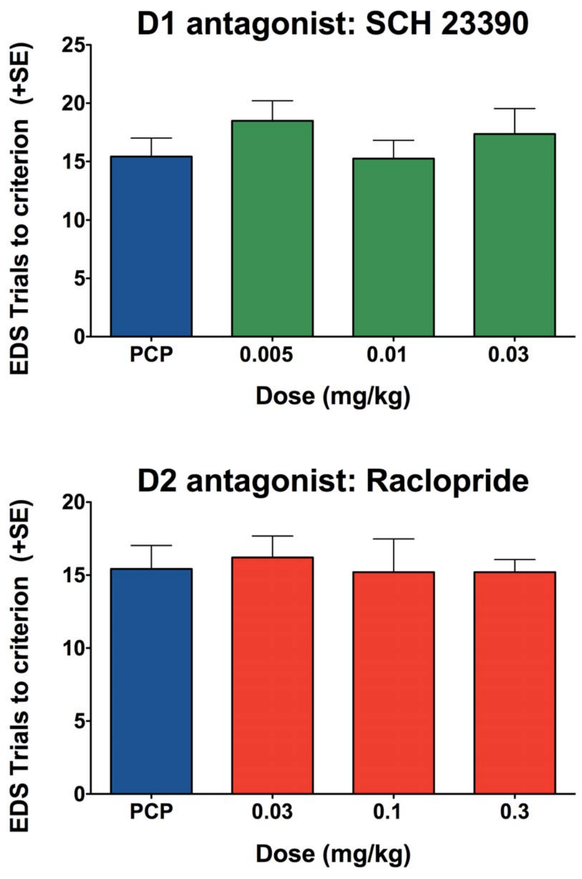


Figure 2. SCH 23390 & raclopride do not significantly alter the PCP-induced EDS deficit

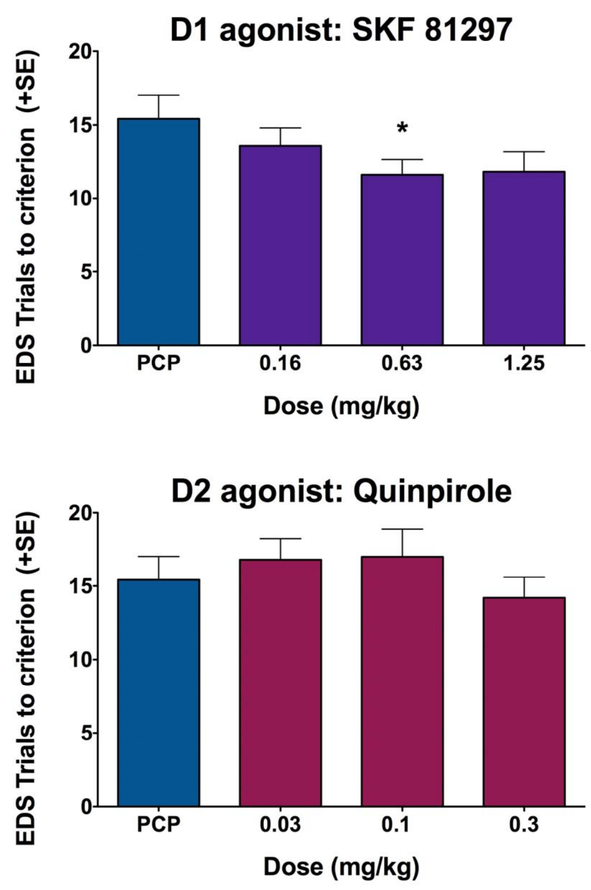


Figure 3. SKF81297, but not quinpirole, alters significantly the PCP-induced EDS deficit

Conclusions

- **DA receptor subtypes contribute differentially to cognitive improvement in this subchronic PCP model of deficits.**
- **The D1 agonist SKF 81297 was the most effective in attenuating the impairment produced by subchronic PCP.**
- **Thus, there may be distinct roles for different dopamine receptors in the capacity to modify cognitive flexbility.**

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