ever, a trend towards decreased activity was evident for raclopride, although this was not statistically significant due to a high standard deviation as a result of the marked effect of the compound.

## 4. Discussion

The main finding of this study was that all compounds tested, with the exception of sertindole, disrupted the performance of the task, suggesting that most, but not all, types of antipsychotic drugs disturb cognitive functioning in rats.

To ensure comparability of the drug effects between the two different strains of rats used, clozapine (2.5 mg/kg) and haloperidol (0.040 mg/kg) were tested in both strains. Overall, the effect of these two compounds in the two strains was comparable. Wistar rats compared to Long-Evans rats were slightly more sensitive to haloperidol but somewhat less sensitive to clozapine. Long-Evans rats were included in the study in order to investigate if the variability among rats was

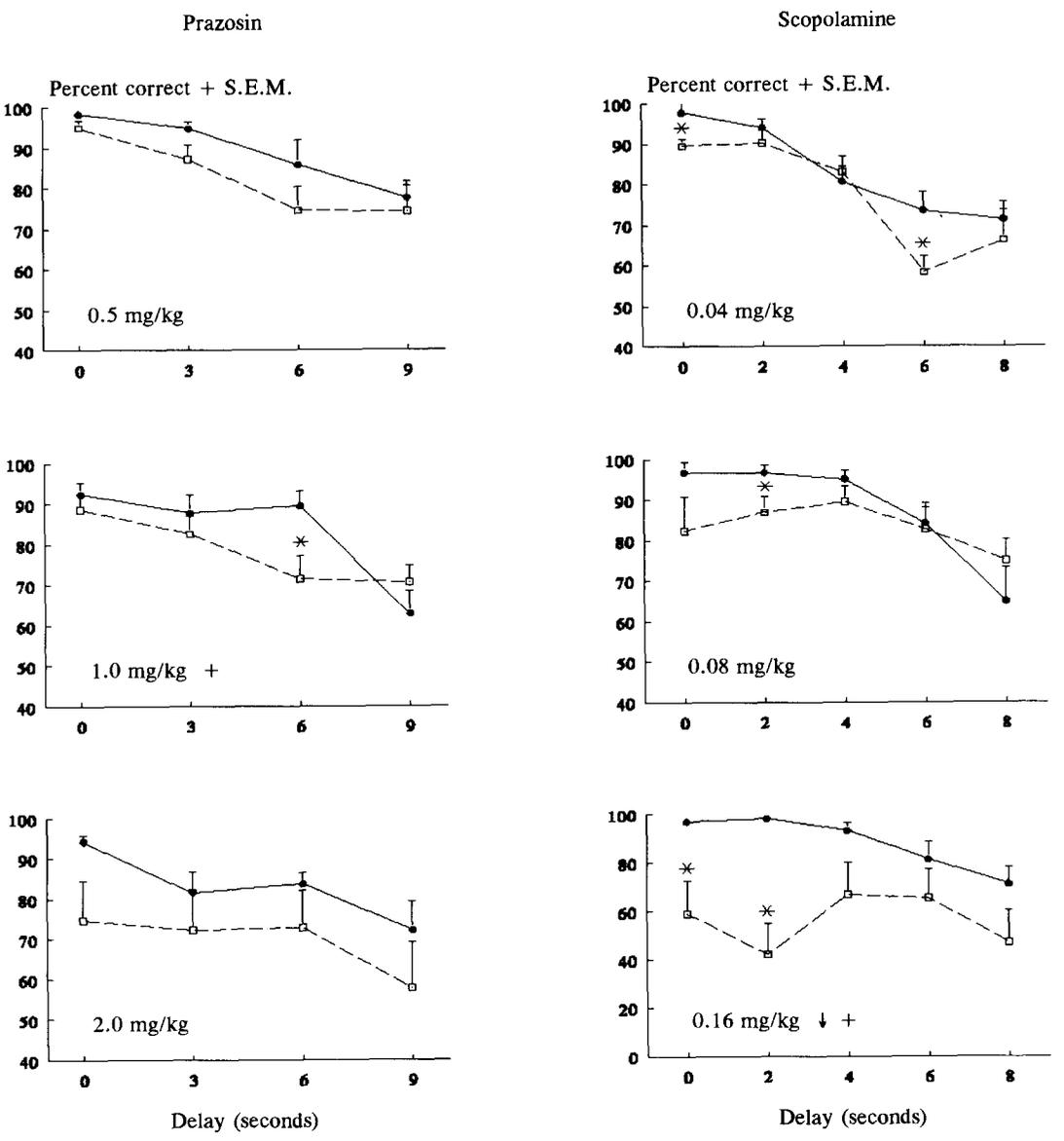


Fig. 5. Delayed non-match to position performance of rats following injection of prazosin (A) or scopolamine (B). The results are presented as means in percent + S.E.M. as a function of delays measured in seconds. $^{*}P < 0.05$ versus control day, by 1-way ANOVA with day as within factor. ↓ and + placed next to the dose tested indicate a significant decrease and a day × delay interaction, respectively, calculated by 2-way ANOVA with day and delay as within factors. ● Control day, □ test day.

smaller in an inbred strain. The variability among rats in the two strains was of the same magnitude. Consequently, in future studies Wistar rats will be used.

The effect of the compounds on the performance of the task depends on their receptor profile. Blockade of the dopamine $D_1$ receptor subtype by SCH 23390 induced a specific inhibition of working memory as the inhibition was delay dependent. Furthermore, a motor or motivational inhibition was induced, as indicated by the reduction in the number of trials and intertrial interval responses. The number of errors in steps 1–5 (Fig. 1) was slightly increased. The dopamine $D_2$ receptor antagonists raclopride and haloperidol disrupted the performance in the choice stage, independent of the delays selected. Moreover, all other parameters measured were reduced, especially the index of unspecific performance. The antipsychotics with mixed receptor profiles clozapine, sertindole, and risperidone affected the performance of the task differently. The effects of clozapine and risperidone were similar and comparable to the effects of the dopamine $D_2$ blocking compounds, while sertindole was ineffective. In vitro, sertindole has a high affinity for dopamine $D_2$ receptors (Sánchez et al., 1991); however, in acute in vivo tests for dopaminergic antagonism sertindole is remarkably weak or ineffective (Sánchez et al., 1991; Skarsfeldt, 1992). Another reason for the lack of effect of sertindole might be the relatively short time (30 min) between the injection and the testing of the compound. However, sertindole was also ineffective in the high dose 2 h after administration.

Clozapine, sertindole, and risperidone all block the 5-$HT_2$ receptor. Sertindole may be considered as a control for 5-$HT_2$ receptor blockade relative to dopamine $D_2$ receptor blockade since a 5-$HT_2$ antagonism occurs at doses well below those inhibiting

Table 1
Drug effects on trials, index of unspecific performance and intertrial interval responses

| Parameter / Compound | Trials | Index of unspecific performance | Intertrial interval responses |
|---|---|---|---|
| Control range | 51–59 | 0.62–0.88 | 11–30 |
| SCH 23390 | | | |
| 0.005 mg/kg | 57 | 0.85 | 13 |
| 0.01 | 53 | 0.77 | 12↓ |
| 0.02 | 28↓ | 0.59↓ | 4↓ |
| Raclopride | | | |
| 0.02 mg/kg | 57 | 0.86 | 17 |
| 0.04 | 54 | 0.68 | 13 |
| 0.08 | 15↓ | 0.31↓ | 6 |
| Haloperidol | | | |
| 0.01 mg/kg | 57 | 0.85 | 10 |
| 0.02 | 51↓ | 0.66 | 23 |
| 0.04 L | 53↓ | 0.28↓ | 14↓ |
| 0.04 W | 23↓ | −0.01↓ | 7↓ |
| Clozapine | | | |
| 0.63 mg/kg | 53 | 0.68 | 18 |
| 1.25 | 54 | 0.63 | 20 |
| 2.50 L | 38↓ | 0.20↓ | 16 |
| 2.50 W | 50 | 0.48↓ | 22 |
| Sertindole | | | |
| 0.04 mg/kg | 55 | 0.74 | 12 |
| 0.16 | 58 | 0.86 | 9 |
| 1.25 | 58 | 0.90 | 8 |
| Risperidone | | | |
| 0.1 mg/kg | 54 | 0.58 | 17 |
| 0.2 | 49 | 0.53↓ | 13 |
| 0.4 | 18↓ | −0.15↓ | 5↓ |
| Prazosin | | | |
| 0.5 mg/kg | 56 | 0.62↓ | 8↓ |
| 1.0 | 53 | 0.65 | 10↓ |
| 2.0 | 49 | 0.37 | 14↓ |
| Scopolamine | | | |
| 0.04 mg/kg | 55 | 0.52 | 18 |
| 0.08 | 40↓ | 0.24↓ | 14 |
| 0.16 | 29↓ | −0.37↓ | 9↓ |

Results are presented as the means from the test day. ↓ significant decrease versus control day for the respective group, by 1-way ANOVA with day as within factor. The control range is represented by the lowest and highest control values found. (L) Long-Evans, (W) Wistar.

dopaminergic or $\alpha_1$-adrenergic mechanisms (Arnt, 1992; Hyttel et al., 1992). Thus, 5-$HT_2$ receptor antagonism seems not to have any consequences for the performance of this task, a conclusion supported by the results of Sawaguchi and Goldman-Rakic (1991). They showed that local injection of ketanserin, a 5-$HT_2$ receptor antagonist, into the prefrontal cortex was without effect in a spatial working memory task for monkeys.

Clozapine, sertindole, and risperidone all block the $\alpha_1$-adrenoceptor. In order to exclude this effect as being responsible for the deficits, the $\alpha_1$-adrenoceptor antagonist prazosin was studied. Prazosin did not affect working memory; however, a reduction in the intertrial interval responses was found without any reduction in the number of trials, possibly indicating a reduced impulsivity. It may be suggested that a decreased number of responses during the intertrial interval indicates an increased adaptation to the nature of the task as these responses are punished. If so, it would be reasonable to expect an improved performance. No improvement was found and it is not likely that such an effect was induced.

The differential effects of dopamine $D_1$ versus $D_2$ receptor antagonism were expected. The dopamine $D_1$ receptor is the predominating dopamine receptor subtype in the frontal cortex (for a review of dopamine and the regulation of prefrontal cortical function see Dolan and Grasby, 1994), whereas the dopamine $D_2$ receptor subtype is dominating in the hippocampus (Boyson et al., 1986) and more basal parts of the brain. The specific interference with working memory function induced by SCH 23390 may be related to the dominance of the dopamine $D_1$ receptor in the prefrontal cortex. This is supported by the findings of Sawaguchi and Goldman-Rakic (1991), who showed that local injection of SCH 23390 into the prefrontal cortex disrupted the performance of a spatial working memory task for monkeys. A similar effect was not found for either raclopride or ketanserin. The effect of the dopamine $D_2$ receptor blocking compounds may be mediated via the basal structures of the brain, e.g. the hippocampus, which is essential for cognitive functions (Squire et al., 1990). Furthermore, the memory-improving properties of dopamine receptor agonists on tasks sensitive to both hippocampal and caudate lesions are mediated via the dopamine $D_2$ receptor alone (Packard and White, 1989), or the dopamine $D_1$ and $D_2$ receptors in concert (Imperato et al., 1993; Packard and White, 1991). The effect of dopamine on cognitive functions via the hippocampus might be mediated through the action of dopamine on the release of acetylcholine (Imperato et al., 1993). The findings of Imperato et al. (1993) suggest that emotional and motivational drives, mediated by enhanced dopaminergic transmission, may lead to potentiation of attention and cognition. A reduction in motivational drive and attention may account for the reduced activity and index of unspecific performance, respectively, induced by the dopamine $D_2$ receptor blockers. The effects of risperidone and clozapine may be attributed to their effects on the dopamine $D_2$ receptor. Clozapine blocks the dopamine $D_1$ receptor to the same degree as the dopamine $D_2$ receptor (Farde et al., 1989) and the dopamine $D_1$ effect may be superimposed on the dopamine $D_2$ effect. However, the affinity of clozapine for dopamine $D_1$ and $D_2$ receptors is relatively small compared to its affinity for muscarinic receptors (Fitton and Heel, 1990). Therefore, the anticholinergic profile of clozapine might be the main reason for its effect since the profile of scopolamine in the present test and that of clozapine are comparable. This is supported by the work of Goldberg et al. (1993), who reported that antipsychotic treatment with clozapine is associated with a decline in some memory functions, an effect that is assigned to anticholinergic properties. Another possibility might be a combination of all the effects of clozapine. The lack of response of sertindole is in agreement with the lack of acute antidopaminergic action in vivo (Sánchez et al., 1991; Skarsfeldt, 1992). There is no ready explanation for why the $\alpha_1$-adrenoceptor antagonistic action alone as well as the relative affinities for 5-$HT_2$ receptors, $\alpha_1$-adrenoceptors and dopamine $D_2$ receptors of sertindole do not contribute to an inhibitory effect. The relative affinities might in fact be responsible for the lack of effect.

Most of the compounds tested in the present study have been tested in comparable doses in the Morris water maze (Scheel-Krüger, 1992), another animal model of cognitive function. In the water maze, SCH 23390, raclopride, and haloperidol also induced an impairment of performance, whereas sertindole was without effect. However, clozapine induced no disturbances at high dose levels (5–7.5 mg/kg), but rather an improvement after low doses (1–2.5 mg/kg), contrary to the present findings. Placing the animals in the water maze is far more stressful than placing the animals in the present test equipment and, accordingly, the initial induced stress may overcome a 'behavioural' blockade induced by the compound. In this case, clozapine does not disrupt the memory function but rather induces an initiation problem. The discrepancy between the tests demonstrates the importance of using several behavioural models when elucidating the activity profiles of drugs.

Improvement of psychiatric symptoms is not associated with major improvement of cognitive functions (Addington et al., 1991; Goldberg et al., 1993). This is not surprising based on the present results. The efficacy of antipsychotic treatment is mainly attributed to the improvement of positive rather than negative symptoms. Addington et al. (1991) found that cognitive