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Antipsychotic and anticholinergic effects on two types of spatial memory in schizophrenia

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Abstract

Spatial memory is of interest in schizophrenia because of widespread impairments in adaptive functioning, including independent living skills. Short-term spatial memory is impaired in this disease, whereas spatial reference memory, a longer-term spatial memory, has not been evaluated. Animal studies have demonstrated that anticholinergics impair short-term spatial memory but not spatial reference memory. The effects of haloperidol and risperidone on these two types of spatial memory were evaluated in a double-blind randomized comparison in inpatients with schizophrenia. It was predicted that risperidone would have a greater beneficial effect on spatial working memory than haloperidol. Computerized measures of spatial working memory and spatial reference memory were developed based on animal assessment of these functions. Subjects with schizophrenia were assessed during a medication-free period and again following 4 weeks of fixed-dose treatment. Risperidone, compared to haloperidol, improved spatial working memory performance, an effect that became nonsignificant when benztropine co-treatment was controlled. There were no treatment effects on spatial reference memory performance. Consistent with animal studies, benztropine impaired spatial working memory but not spatial reference memory. The relative benefits of risperidone on spatial working memory performance were largely explained by differential benztropine treatment for the haloperidol-treated subjects.

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1. Introduction

One aspect of spatial information processing of interest in schizophrenia is place memory. Short-term place memory, or spatial working memory, has been

shown to be impaired in schizophrenia (Park and Holzman, 1992; Keefe et al., 1995). Spatial working memory deficits in schizophrenia have been demonstrated using delayed response tasks requiring the short-term memory of a spatial location in order to guide a response at the end of a brief delay (Goldman-Rakic, 1994). The to-be-remembered information in delayed response tasks is updated trial by trial.

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In contrast to spatial working memory tasks, spatial reference memory tasks involve the acquisition of rules about spatial locations that are constant across all trials of the task. Spatial reference memory has been well-studied in animal paradigms that assess the acquisition of spatial rules. Examples of these paradigms include the radial arm maze in rats (Olton, 1987), where designated arms of the maze are never baited with food, and operant spatial discrimination tasks, where levers in specific locations are never associated with appetitive reward (Bustnell, 1990). In these tasks, the response that indicates the acquisition of the spatial rule is the avoidance of those never-rewarded places.

Human studies assessing place memory have shown that both declarative processes (Pezdek and Evans, 1979) and implicit, or procedural processes, may be involved in the long-term retention of spatial locations (Glassman et al., 1998). Although implicit memory, such as word priming (Perry et al., 2000) and motor sequence learning (Green et al., 1997a), have been evaluated in schizophrenia, spatial reference memory has not.

Place memory is of interest in schizophrenia because this cognitive domain is utilized in every day activities, such as taking public transportation and other activities of daily living, that are impaired in this illness. Place memory is also of interest in schizophrenia because it is affected by pharmacological treatments used in this disorder. Anticholinergic drugs, which are commonly used to treat neuroleptic-induced side effects, impair spatial working memory as assessed in a variety of paradigms and populations. For example, performance deficits caused by anticholinergic drugs have been demonstrated using T-maze alternation (Moran, 1993) and radial arm mazes in rats (McGurk et al., 1988; Levin et al., 1997), delayed response tasks in nonhuman primates (Bartus and Johnson, 1976) and short-term memory for object shape (Robbins et al., 1997) and object location in humans (Flicker et al., 1990). Rat studies have shown that anticholinergics cause only weak (Bustnell, 1990) or no impairment of spatial rule acquisition (Beatty and Beirley, 1985; Givens and Olton, 1994; Levin et al., 1997), a cognitive area that has not been evaluated in nonhuman primates or humans.

Several studies have reported on the effects of antipsychotic on spatial memory or related domains

in schizophrenia. For example, delayed matching to sample, an index of short-term, object memory, was impaired by haloperidol in patients with schizophrenia (Levin et al., 1996). Clozapine, a new generation antipsychotic, impaired visual memory for designs in patients with schizophrenia, an effect that was postulated to be due to the anticholinergic properties of this drug (Goldberg and Weinberger, 1994). Olanzapine was found to have no effect on spatial working memory in outpatients with schizophrenia (Meltzer and McGurk, 1999). Hutton et al. (2001) found no differences in spatial memory performance in first-episode patients with schizophrenia who were either unmedicated or receiving antipsychotics, with approximately 40% receiving atypical antipsychotics. In prior publications from the currently reported study, risperidone, but not haloperidol, improved verbal working memory (Green et al., 1997b), and verbal learning and memory (Kern et al., 1999). Beneficial effects of risperidone on these two types of verbal memory were not explained by indirect mechanisms such as clinical symptom change or differential co-administration of benztropine in patients receiving haloperidol. Therefore, the mechanism of risperidone's ability to improve these cognitive domains may be due to direct pharmacological mechanisms, such as affinity for the 5HT_{2a} receptor, which enhances dopaminergic turnover in the frontal cortex (Schotte et al., 1996), and which haloperidol lacks. Neither drug improved performance on the serial reaction time, a measure of implicit, sequential, motor learning (Kern et al., 1998).

The current report is an evaluation of the effects of haloperidol and risperidone on two types of spatial memory: spatial working and reference memory. It was predicted that risperidone would have a greater beneficial effect on spatial working memory than haloperidol. Neither drug was predicted to improve spatial reference memory.

2. Method

Data in the current report were obtained from a double-blind study of the clinical efficacy, side-effect liability and neurocognitive effects of risperidone vs. haloperidol in treatment-resistant schizophrenia. Data from this study have been published on measures of

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