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Short Communication

The involvement of distraction in memory deficits induced by NMDAR antagonism: Relevance to cognitive deficits in schizophrenia

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HIGHLIGHTS

- We investigate the effects of varying the ITI on sub-chronic PCP-induced NOR deficits.
- Sub-chronic PCP treated rats successfully encode acquisition trial information.
- Sub-chronic PCP treated rats demonstrate object discrimination only if left undisturbed during the ITI.
- Sub-chronic PCP treated rats exhibit enhanced susceptibility to distraction.

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ABSTRACT

Recognition memory, impaired in neuropsychiatric conditions and currently untreated, may be assessed by the novel object recognition (NOR) task with robust impairments induced by sub-chronic treatment with the *N*-methyl-D-aspartate receptor antagonist phencyclidine (PCP). The aim of the present study was to investigate how sub-chronic PCP produces its effects in this task. Forty adult female rats received vehicle or PCP (2 mg/kg i.p. twice daily for 7 days followed by 7 days washout). Rats completed a 3-min acquisition trial followed by differential inter-trial-interval (ITI) conditions (1 min in the home cage, 10 s in the home cage, 1 min in the NOR test box in the presence of an unfamiliar object or 1 min in the NOR test box completely undisturbed) followed by a 3-min retention trial. Control rats spent significantly more time exploring the novel compared with the familiar object in retention. This effect was abolished in the sub-chronic PCP treated animals following all ITI conditions except in rats left completely undisturbed in the NOR test box for a 1 min ITI. The combined influence of sub-chronic PCP treatment and the effect of distraction provides further support for the validity of the NOR test in mimicking cognitive deficits of relevance to schizophrenia.

1. Introduction

Cognitive dysfunction is an unmet clinical need in schizophrenia and one of the main determinants of patients' functional outcome [1,2]. Recognition memory is one particular domain affected in these patients [3,4]. Interestingly, schizophrenia patients are more susceptible to distraction during visual memory tests when compared with control subjects [5,6].

The need to design, develop and thoroughly validate paradigms to assess the various cognitive domains disrupted in schizophrenia in preclinical tests is critical since as yet, no medication has been licensed to treat these particularly debilitating symptoms. The NOR test in rodents measures visual learning and memory and is recommended by MATRICS as a test to assess cognitive disturbances of relevance to schizophrenia [7]. It is ethologically relevant, does not require training or food restriction and uses the rodents' natural affinity for novelty, that is, rats show a preference for exploration of a novel compared with a familiar object [8]. The inter-trial-interval (ITI) period, between the acquisition and retention trial, can be manipulated to modify the cognitive load and determine the specific brain region of interest [9]. For example, lesion studies in the mouse have demonstrated that, when the hippocampus is

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inactivated, impaired object recognition is observed at relatively long (24 h) but not short (5 min) ITIs, whereas the perirhinal cortex/pre-frontal cortex (PFC) is believed to be responsible for recognition memory following ITIs of less than 5 min [9,10].

Previous research in our laboratory [11] and others [12–14] has shown that sub-chronic treatment regimens with NMDAR antagonists, such as phencyclidine (PCP), induce reliable cognitive impairments in rodents. Sub-chronic PCP can be used to model cognitive impairments in schizophrenia as evidence suggesting that NMDAR hypofunction is central to pathology of this illness [11]. However, it is unclear why and how PCP produces its cognitive deficits in many tests, information essential for understanding the translational relevance of this model.

The aim of the present studies was therefore to examine the effects of modifications (ITI time, location and distraction) to the novel object recognition (NOR) test procedure on PCP-induced memory impairment.

2. Materials and methods

2.1. Animals

Forty adult female hooded-Lister rats (Charles River, UK) weighing 210 ± 14 g housed in groups of five under a constant temperature of 21 ± 1 °C and humidity (40–50%) under a 12-h light:dark cycle, lights on at 0700 h, were used as subjects. Studies were carried out in accordance with the Animals Scientific Procedures Act (UK, 1986) and approved by the local University Ethical Review process.

2.2. Drug administration

Rats were randomly selected to receive either the vehicle (n = 20, 0.9% saline) or PCP hydrochloride (n = 20, 2 mg/kg) both twice a day, i.p. for 7 days, followed by 7 days washout [11]. The 7-day washout period is necessary to prevent behaviour being influenced either by direct drug effects or by drug withdrawal effects.

2.3. Apparatus

The apparatus is described in detail in Grayson et al.; a total of five identical NOR boxes were used for these studies [15].

2.4. Habituation

Rats were habituated in cage groups to the empty NOR apparatus and test room environment for three consecutive days for 20 min, with a habituation day directly preceding the test day.

2.5. Behavioural testing

All 40 rats were randomly assigned to experiment 1 or 2 and tested on Monday, 20 per experiment n = 10 PCP and 10 vehicle treated. Then, all rats were randomly re-assigned to experiment 3 or 4 and tested three days later. The experiments took 1 week to complete in total. A further 3-min habituation session in the NOR box preceded the acquisition trial on the day of testing. Each rat was placed in the box and exposed to two identical objects (A and B) for a period of 3 min during the acquisition trial, which was followed by the differential ITI conditions. Following the ITI, the novel and familiar (triplicate of the objects seen in the acquisition trial) objects were replaced immediately for the retention trial. The location of the novel object in the retention trial was randomly assigned.

In experiment 1, the rat was placed for 1 min in the home cage for the ITI (normal conditions [11,15]). To assess whether time was a factor, for experiment 2, the rat was placed in the home cage for 10 s for the ITI. To test the effect of a distracter, during experiment 3, an unfamiliar object was placed in the centre of the NOR box during a 1 min ITI in which the rat remained in the NOR box. The object was removed prior to the retention trial. The object, a wooden cone, was carefully selected on the basis of previous studies in our laboratory showing that the time spent exploring the wooden cone was significantly greater compared with the other objects. Along with the possibility of time being a potential contributor to the deficits seen, the location of the rats during the ITI could also contribute. To explore this possibility, in experiment 4, the rat was left in the NOR box for an ITI of 1 min with no objects present. Object exploration was defined as the rats sniffing, licking or touching the objects with forepaws whilst sniffing but not leaning against, turning around, standing or sitting on the objects [8]. The exploration time (s) of each object in each trial was recorded manually and the DI was calculated. The DI represents the difference in time spent exploring the novel and familiar objects. Line crossings were also recorded and all the experiments were scored by an experimenter blind to treatment.

2.6. Statistical analysis

Data are expressed as the mean ± S.E.M. and analysed by two-way ANOVA. Further analysis by Student's t test was carried out to compare the time spent exploring the novel and familiar objects. DI and line crossing data were analysed by a one-way ANOVA, followed by a post hoc Dunnett's t test as previously described [18].

3. Results

3.1. Acquisition trial

There was no significant effect on time spent exploring the two identical objects in any of the groups (data only shown therefore for the first experiment; see Fig. 1a).

3.2. Experiment 1; 1 min ITI in the home cage (normal conditions)

Vehicle control rats spent significantly (P < 0.001) more time exploring the novel compared with familiar object during the retention trial following the 1 min ITI within the home cage, our standard conditions (Fig. 1b). This significant preference for the novel object was not observed in sub-chronic PCP-treated rats, i.e. these rats spent a similar amount of time exploring both objects (Fig. 1b). Sub-chronic PCP significantly reduced the DI compared with vehicle treated rats (P < 0.05; Fig. 1c).

3.3. Experiment 2: 10 s ITI in the home cage

As in experiment 1, vehicle rats spent significantly (P < 0.05) more time exploring the novel compared with the familiar object during the retention trial following a 10 s ITI within the home cage. This significant preference for the novel object was not observed in sub-chronic PCP treated rats, i.e. these rats spent a similar amount of time exploring both objects (Fig. 2a). The reduction in DI following sub-chronic PCP did not reach statistical significance (Fig. 2b).

3.4. Experiment 3: 1 min ITI in the NOR box with an unfamiliar object

Vehicle treated rats spent significantly (P < 0.001) more time exploring the novel compared with familiar object during the retention trial following a 1 min ITI in the NOR test box with an unfamiliar object (the wooden cone) present. This significant preference in the vehicle treated rats for the novel object was not observed in the PCP