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Research report

Nigral 6-hydroxydopamine lesion impairs performance in a lateralised choice reaction time task—Impact of training and task parameters

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HIGHLIGHTS

- Nigral 6-OHDA lesion impairs the performance in a choice reaction time task.
- Same pattern of deficits as after striatal and bundle 6-OHDA injections.
- Pretraining resulted in a more robust data set with less preservative errors.
- Shorter holds reduced the rate of premature withdrawals compared to longer holds.

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ABSTRACT

Unilateral intrastriatal and intra-medial forebrain bundle injections of 6-OHDA impair the performance in a lateralised choice reaction time task. However, the extent and pattern of deficits after nigral 6-OHDA injections is less well studied, as well as the impact of training regime or the modification of various task parameters.

The nigral 6-OHDA lesion resulted in impaired response accuracy and an increased time to react to and execute the response on the side contralateral to the lesion as compared to sham-lesioned controls. Pre-training of the rats on the task prior to the lesion resulted in slightly faster reaction times as well as a reduced number of preservative panel presses compared to when rats were trained after the 6-OHDA injection. When the rat had to perform a longer sustained nose poke before responding to the lateralised stimuli, the number of useable trials was reduced in both controls and 6-OHDA rats as a result of an increased number of premature withdrawals from the centre hole.

This study demonstrates that rats with a nigral 6-OHDA lesion display several distinct deficits in this operant task, which are similar to those seen after striatal and bundle 6-OHDA injections. In addition, by combining pre-training with the use of a short set of holds, improved sensitivity of this task can be achieved. This improvement in sensitivity may be of advantage when exploring new therapeutic interventions for PD, where subtle but relevant changes in performance may arise.

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1. Introduction

Loss of striatal dopamine (DA) as a result of degenerating DA-ergic neurons in the substantia nigra pars compacta (SNpc) is one of the pathological hallmarks of Parkinson's disease (PD), causing the characteristic motor symptoms of the disorder [1]. It has recently become apparent that patients with PD also suffer from a myriad of non-motor symptoms [2], which strongly contribute to a reduced quality of life [3]. One example is visuospatial deficits [4], exemplified by difficulties navigating through confined spaces and interacting with objects in their environment [5,6].

Unilateral 6-hydroxydopamine (6-OHDA) rodent and non-primate models of PD show similar impairments in detecting and responding to stimuli on the side contralateral to the lesion [7–11]. Carli et al. were first to describe that striatal unilateral 6-OHDA lesions impair performance in an operant lateralised choice reaction time task (CRT [9]) in which the rats are required to make a sustained nose poke in the central hole of a nine-hole box apparatus (9HB) following presentation of a stimulus light in the same hole [12]. After variable delays, a brief stimulus light is randomly presented on either the left or right side of the animals' head, and

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the rats are required to nose poke into the corresponding hole. Unilateral injections of 6-OHDA into the striatum impairs the ability to respond to the lateralised stimuli on the side contralateral to the lesion and it was suggested that the depletion of DA disrupts spatial representation of the environment, important for appropriately directing movements in contralateral space [8]. Similar pattern of deficits in the CRT task but more severe in extent were also found after medial forebrain bundle (MFB) 6-OHDA lesions [13,14]. Injections of 6-OHDA can also be made at the origin of the MFB, i.e. the SNpc, which results in a more specific and moderate DA depletion. Only one study has utilised rats with nigral 6-OHDA lesion in the CRT task [15] but this study did not characterise the full array of deficits after this type of 6-OHDA injection.

Previous studies utilising the CRT task have only examined the effect of 6-OHDA in rats that were trained on the task prior to the lesion [10,13]. There is, however, compelling evidence from PD patients that the striatum and DA are necessary for certain types of stimulus–response (S-R) learning (reviewed in ref. [16]), and the clinical data is supported by converging evidence from animal studies [17–19]. Therefore, it is relevant to also evaluate the effect of training on the end performance in the lateralised CRT task after nigral 6-OHDA lesions.

The CRT task requires the rat to make and hold a nose poke in the centre hole for a certain amount of time. Different studies have used various sets of holds, ranging from very short (50–200 ms [10]) to slightly longer (200–800 ms [13]) and even to very long holds (0–1500 ms [9]). It has been shown that length of the holds affects the time it takes for the rat to react to lateralised stimuli, namely that longer fore periods results in shortening of the reaction time [20,21]. Interestingly, it has also been shown that the delay-dependent speeding of the reaction time is DA dependent since it is abolished after unilateral DA depletion [20] and enhanced after amphetamine administration [21]. However, the effect of the different holds on the other parameters assessed in this task has not yet been made.

The aim of the current study was to fully establish the extent and pattern of deficits after a nigral 6-OHDA lesion in the lateralised CRT task. In addition, the impact of training and the use of different hold durations on the performance in the task were evaluated. To this end, rats were trained on the lateralised choice reaction time task prior to or after a nigral 6-OHDA lesion and thereafter tested in the lateralised CRT task utilising both a short (50–200 ms) and a longer (200–800 ms) sets of holds.

2. Materials and methods

2.1. Animals

Female Lister hooded rats (220–250 g, Charles River, Margate, Kent, UK) were housed in groups of four per cage under a 14-h light:10-h dark cycle and controlled temperature (20 °C). All rats were allowed *ad libitum* access to water during the study but were food-restricted to 85–90% of their free feeding weights, starting one week prior to each experiment. All experiments were conducted in accordance with the UK Animals (Scientific Procedures) Act 1986, with local ethical review and under Home Office personal and project licenses.

2.2. Experimental design

A total of 32 rats were used in this study and the experimental design is shown in Fig. 1. A subset of rats was pre-trained (PT-cohort) on the lateralised CRT task until a stable baseline was established (six weeks of training, data not shown), before receiving a 6-OHDA lesion ($n = 7$) or sham lesion ($n = 8$). One month after the lesion, the rats were re-tested in the operant boxes. Another subset of rats received either a 6-OHDA ($n = 9$) or sham lesion ($n = 8$) one month *before* being trained on the CRT task for six weeks (nonPT cohort, training data not shown). After this time point, i.e. when a stable baseline in the CRT task had been established in both cohorts but prior to or after the 6-OHDA lesion for respective cohort, all rats were tested in two different probe trials. In the first trial, the rats were tested for five days in an easier version of the task compared to the baseline performance (the rats had to keep the sustained nose poke in the centre hole for a shorter range of time; "short holds"). Thereafter, the rats were tested in a second probe trial for five days in which the task parameters, i.e. the length of the holds, were the same as in the baseline training but accordingly longer than in the first probe trial ("long holds"). Both cohorts of rats were also assessed in simple tests of motor asymmetry i.e. the cylinder test and amphetamine-induced rotations.

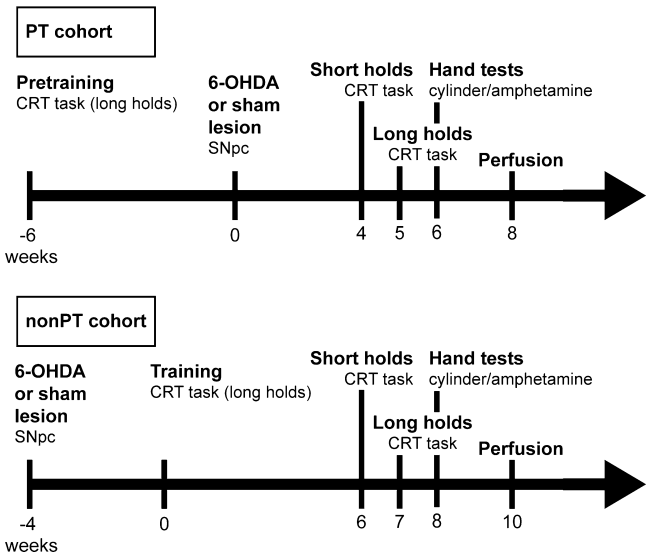

Fig. 1. Schematic illustration of the experimental design applied in this study. CRT: choice reaction time task.

2.3. 6-OHDA lesions

Anaesthesia was induced using 3–4% isoflurane with a 2:1 mixture of nitrous oxide and oxygen as carrier gases, and withhold at 1.5–2% during the surgery session. Rats were mounted in a Kopf stereotaxic frame using atraumatic ear bars and the nose bar was set at −3.3 mm below the interaural line. A midline incision was made in the skin overlying the skull. A small hole was drilled at the following coordinates: AP = −5.3 and ML = −1.7 from bregma [22]. 6-OHDA (8 μg in 2 μl of 0.9% saline containing 0.05% ascorbic acid; Sigma–Aldrich, Gillingham, Kent, UK) or saline were infused at DV = −7.2 from dura via a 30-gauge metal cannula with a flow rate of 1 μl/min, and left to diffuse for a further 2 min before removal of the cannula. Following surgery wounds were cleaned and sutured and rats received 30 μl Metacam (5 mg/ml, Boehringer Ingelheim, Germany) subcutaneously for pain relief and glucose–saline to reduce postoperative dehydration. Rats were allowed to recover in a heated cage.

2.4. Behavioural tasks

2.4.1. Lateralised choice reaction time (CRT) task

The lateralised choice reaction time task, as first described by Carli et al. [9], requires the rat to make a lateralised response after a sustained centralised nose poke. The lateralised CRT task was conducted in a bank of twelve identical 9HB operant chambers,

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