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Medial prefrontal cortex lesions in mice do not impair effort-based decision making

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ABSTRACT

The function of the medial prefrontal cortex has previously been determined in the rat to play an important role in effort-based decision making and this, along with functions of other areas, has been assumed largely, to hold true in all rodents. In this study, we attempted to replicate this result in mice and to develop a model for effort-based decision making that could be useful for the study of neurological conditions. Mice were trained on a cost-benefit T-maze paradigm, whereby they chose between a low reward with little effort needed to obtain it or a higher reward, which required increased effort. Following training, the medial prefrontal cortex was lesioned. After surgery, contrary to earlier published rat studies, the performance of the mice did not change. In previous studies, prefrontal cortex lesioned rats chose the low effort/low reward option, but lesioned mice continued to select the high reward/high effort option. However, the other results are in line with previous mouse studies in both the extent of pathology and anxiety-like behaviour. These results illustrate a difference in the functioning of the prefrontal cortex between rats and mice and offer a word of caution on the interpretation of data from studies that employ different species.

1. Introduction

The mouse has become the animal of choice for many in vivo studies due to the ease of manipulation of its genome. However, in neuroscience and modelling CNS conditions, most of our knowledge comes from studies using rats. It is therefore important to ensure this knowledge holds true for and is transferable to mice. Interestingly, species differences have previously been demonstrated. For example, McNamara et al. (1996) showed both molecular, in the hippocampus, and behavioural differences between rats and mice.

Modelling neurological conditions is difficult at the best of times and one has to be cautious not to over-interpret or extrapolate too far from findings. There are transgenic and lesion models for many neurological conditions such as schizophrenia, Alzheimer's disease, depression etc. As a result many specific brain areas have been linked to the pathogenesis of these conditions, such as the hippocampus in Alzheimer's disease (Braak et al., 1993) and the prefrontal cortex to nucleus accumbens projections in schizophrenia (Carr et al., 1999; Csernansky et al., 1991). Indeed the prefrontal cortex has also been shown to have a role in conditions other than schizophrenia, such as drug addiction (Lasseter et al., 2010) and depression (Bennett, 2011).

However, unlike in rats, the role of the prefrontal cortex in mice has had only limited characterisation, though research in this area has recently increased. Similar to rats, the mouse prefrontal cortex is important for spatial working memory, but this is by no means straightforward (Jones, 2002). The role of the mouse prefrontal cortex has been further elucidated by different groups showing, for example, decreased anxiety-like behaviour (Deacon et al., 2003) and impaired attentional performance (Dillon et al., 2009) following medial prefrontal cortex lesions.

Salamone investigated the role of nucleus accumbens dopamine in rats, using a T-maze cost/benefit paradigm, whereby the rat must distinguish between a high or low reward, irrespective of the amount to effort required to obtain the reward (Salamone et al., 1994). Depletion of the accumbens dopamine caused a reduction in the choice of the high reward, when increased effort was needed to obtain the reward. Work by Walton et al. (2003, 2002) examined lesions in the prefrontal cortex in a T-maze paradigm, based on that of Salamone. Similarly, the choice was between a high effort/high

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reward arm and a low effort/low reward arm. Rats with a lesioned medial prefrontal cortex chose the low effort, low reward arm and it was shown this was as a result of the effort required rather than insensitivity to the level of reward. This showed the importance of the medial prefrontal cortex and, in particular, the anterior cingulate, in effort-based decision making (Walton et al., 2003, 2002).

Since executive decision making is impaired in patients with different cognitive disorders, has been linked to the prefrontal cortex (for review see Reichenberg and Harvey, 2007) and these observations are consistent with the rat lesion data, it would be important to develop a mouse model that could be used to further examine this brain area. In addition, a mouse model would be useful to allow examination of the role of risk genes for neurological conditions in conjunction with the role of the prefrontal cortex.

The aim of this study, therefore, was to translate the rat model of an effort-based decision paradigm into mice and to examine anxiety-like behaviour to show that the findings were in line with previous mouse data (Deacon et al., 2003). While in some cases, particular areas of the prefrontal cortex have been studied, we have not restricted ourselves to any one specific area in this case and instead produced a more general lesion of the prefrontal cortex. This is in line with the original rat model in which the prelimbic, infralimbic and cingulate cortices were affected (Walton et al., 2002).

2. Materials & methods

2.1. Animals

Female C57BL/6 mice (Harlan, UK) were group housed (4–6) in plastic cages with wood chip bedding, under a 12 h light/dark schedule (lights on at 7:00 am). All testing occurred during the light phase of the day. During behavioural testing water was available *ad libitum* but they were food restricted to ~90% of their free-feeding weight. The experiments described were conducted under license from the Department of Health and Children in Ireland and were approved by the Royal College of Surgeons in Ireland research ethics committee. The decision to use only female mice for this work was due to the desire to directly compare with the relevant mouse prefrontal cortex studies (Deacon et al., 2003) and through concern for the welfare of the mice that will be group-housed for a long period of time. Inter-male aggression can be a problem in group-housed C57/BL6 mice, especially if they are not littermates (Betmouni et al., 1999).

2.2. Apparatus

The T-maze used for behavioural testing was based on that described by Walton et al. (2002), but modified for use by mice. The T-maze is a high-sided wooden T-maze, consisting of a start arm and two goal arms all of which are lined by walls, 20 cm high (Fig. 1A). A raised food well was fixed at the far end of each goal arm, equidistant from all sides. The interior walls of the maze were painted black while the floor was grey.

In order to obtain a reward, the mice had to climb over a barrier in the chosen goal arm. The barriers were made out of a heavy wire mesh bent to form a 3 dimensional right-angled triangle. The animals had to scale the vertical side and were then able to descend down the slope to obtain the reward. There were two different height barriers used during testing, namely 5 cm and 10 cm high (Fig. 1B). During validation of the experimental protocol, barriers of greater height than 10 cm were used to determine the height that was most effortful and also the threshold height above which the mice would not climb the barrier. It was found that mice would not climb the barriers that were taller than 10 cm in height.

2.3. Effort-based decision model

2.3.1. Habituation & training

Habituation and training protocols are based on previous work by Walton and are described briefly below (Walton et al., 2002). A summary of the training and surgery timeline is shown in Fig. 2. Prior to habituation and training, the mice were put on a restricted feeding schedule. During the first week, upon reaching 90% of their free-feeding weight, the mice were habituated to the maze both in groups and individually. On completion of habituation all mice were freely running on the maze and eating reward pellets (20 mg MLab Rodent Tablets, Test Diet, Richmond IN, USA) from the food wells.

Discrimination training was run in a number of phases. Phase I involved placing 3 reward pellets in the feeding well of one arm [high reward arm (HR)] and 1 reward pellet in the other [low reward arm (LR)]. For half of the mice, the HR arm was to the right, and for the other half, the HR was to the left. Initially, each mouse was placed in the start arm and sampled the food in each arm before being removed from the maze. There were 3 days of phase I discrimination training and each mouse ran 5 trials per day. The mice were cycled in their cage groups, leaving an intertrial interval of approximately 6 min. Phase II trials were "forced", when access to one of the goal arms was blocked, thus forcing the mouse to sample pellets for a particular arm on each trial. The LR/HR order of the forced trials was determined pseudorandomly so that the mice never had more than two consecutive turns to either side. Mice ran 10 trials per day for 3 days, to complete phase II. Phase III was the final phase and was very similar to phase I. The first two trials for each mouse were forced and then followed by an additional 10 trials. As in Phase I, the mice were allowed a choice of arms in these trials, but instead of being allowed to sample the pellets in each arm, they were removed from the maze after eating the pellets in the first selected arm. When all of the mice were choosing the HR arm on approximately 85–90% of trials in training, a 5 cm barrier was introduced to the maze, placed in the centre of the HR arm. For the first five trials with the barrier, none of the mice were removed from the maze until they had climbed the barrier and eaten the food pellets. In all subsequent training, the trials were run on a strict choice basis and the mice were removed from the maze instantly after consuming food in chosen arm. After three days of 10 trials/day/mouse, the barrier size was increased to 10 cm for a further three days.

2.3.2. Surgery

While in some cases, particular areas of the prefrontal cortex have been studied, we have not restricted ourselves to any one specific area in this case and instead produced a more general lesion of the prefrontal cortex. This is in line with the original rat model in which the prelimbic, infralimbic and cingulate cortices were affected (Walton et al., 2002). Surgery was performed when the mice were ~19 weeks old. They received excitotoxic bilateral mPFC lesions ($n = 13$) or sham surgery ($n = 11$). They were assigned to lesion or sham groups in a counterbalanced way, by virtue of preoperative performance and the right–left orientation of the rewards. All mice were anesthetised with Avertin (2,2,2 tribromoethanol in t-amylalcohol) given at a dose of 0.18 g/kg i.p. They were then placed in a stereotaxic frame (Stoelting,

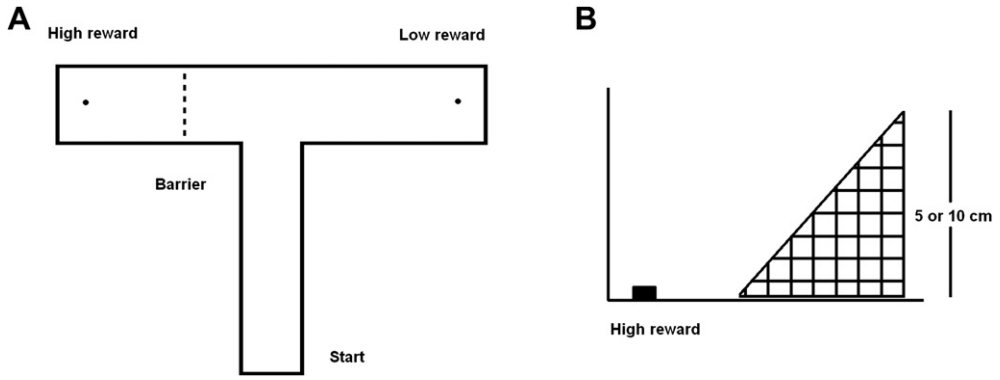

Fig. 1. Pictorial description of the apparatus used in the study. (A) A view from above of the high-walled T-maze used throughout testing, showing where the food rewards are located and where the barrier can be placed. (B) A side-view illustration of the barrier as it would appear in the arm of the T-maze. In order to obtain the reward, mice have to climb the vertical wall of the barrier and descend the slope on the other side.