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A rapidly acquired foraging-based working memory task, sensitive to hippocampal lesions, reveals age-dependent and age-independent behavioural changes in a mouse model of amyloid pathology

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ABSTRACT

Three experiments examined the ability of mice to forage efficiently for liquid rewards in pots located in an open field arena. Search behaviour was unconstrained other than by the walls of the arena. All mice acquired the task within 4 days of training, with one trial per day. Experiment 1 tested the hypothesis that hippocampal lesions would disrupt foraging behaviour using extramaze cues. Mice with hippocampal lesions showed normal latency to initiate foraging and to complete the task relative to sham-operated mice. However, lesioned mice showed increased perseverative responding (sensitization) to recently rewarded locations, increased total working memory errors and an increased propensity to search near previously rewarded locations. In Experiment 2, the extramaze cues were obscured and each pot was identified by a unique pattern. Under these conditions, mice with hippocampal lesions showed comparable working memory errors to control mice. However, lesioned mice continued to display increased perseverative responding and altered search strategies. Experiment 3 tested the hypothesis that age-related accumulation of amyloid would disrupt foraging behaviour in transgenic PDAPP mice expressing the V717F amyloid precursor protein (APP) mutation. Consistent with previous findings, PDAPP mice showed both age-dependent and age-independent behavioural changes. More specifically, 14–16 month-old PDAPP mice showed a deficit in perseverative responding and working memory errors. In contrast, changes in search behaviour, such as systematic circling, were present throughout development. The latter indicates that APP overexpression contributed to some features of the PDAPP behavioural phenotype, whereas working memory and flexible responding was sensitive to ageing and β-amyloid burden. In conclusion, the present study provided novel insight into the role of the hippocampus and the effects of APP overexpression on memory and search behaviour in an open-field foraging task.

1. Introduction

Spatial working memory tasks, such as the radial arm maze and Barnes maze, often take advantage of rodent's natural propensity to forage for food. Such studies have informed our understanding of neural networks involved in spatial navigation and helped characterise the functional properties of hippocampal place cell and entorhinal grid cells in encoding location and movement information (Shapiro et al., 1997; Brunel & Trullier, 1998; Derdikman et al., 2009). There is a growing body of evidence that hippocampal and entorhinal networks are sensitive to the early stages of Alzheimer's disease. For example, hippocampal place cells in amyloid precursor protein (APP) transgenic mice show reduced spatial resolution (Cacucci, Yi, Wills, Chapman, & O'Keefe, 2008; Zhao, Fowler, Chiang, Ji, & Jankowsky, 2014) and mice expressing human tau mutations show disrupted grid cell activity (Fu et al., 2017); similar to individuals possessing an APOE4 genotype (Kunz et al., 2015). Changes in spatial behaviour are well-documented in patients with Alzheimer's disease (Graham, 2015). For example, formal assessment of navigation strategies in patients indicates an early decline in path integration and allocentric memory processes in tasks analogues to the watermaze and the radial maze (Laczó et al., 2010; Lee, Kho, Yoo, Park, & Choi, 2014; Mokrisova et al., 2016). In addition, foraging for rewards in an open field arena has revealed deficits in allocentric memory in patients with Down syndrome, who are at increased risk of developing dementia (Lavenex et al., 2015).

Perhaps the most well-known foraging task is the radial arm maze

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designed by David Olton (Walker & Olton, 1979; Olton, Walker, & Wolf, 1982). In the simplest version of a radial arm maze task, all arms of the maze are baited and the animal has one opportunity to retrieve a food reward from an arm during the trial. As noted by Olton (1987), rodents may adopt a number of different strategies to solve the radial arm maze task. In order to restrict the development of certain spontaneous strategies, such as circling behaviour, rats can be confined to the central hub of the maze between arm selections. While the radial arm maze task can elicit accurate spatial working memory performance in rodents, it can also take several days to achieve such high levels of accuracy (e.g., Clark et al., 2015) and may limit assessment of alternative strategies that may also guide performance.

In the present study, an unconstrained open-field task was used to assess the nature of spontaneous foraging strategies that developed in mice following hippocampal cell loss and in mice developing amyloid pathology with age. The use of an unconstrained procedure can provide insights into the structure of mouse behaviour (c.f., Fonio et al., 2009; Benjamini et al., 2011), the underlying brain circuitry (Gordon et al., 2014) and thus the impact of disease on brain function. The present procedure was based on a task used by Pearce et al. (2005) to investigate foraging behaviour in pigeons. In this task, pigeons were placed in a large open field area and presented with eight food-baited pots, each in different spatial location. Pigeons had to forage the food reward from all eight pots and any return visits to depleted pots during the trial was considered a working memory (WM) error. We have adapted this task for mice using an open arena that contained six pots. Each pot was baited with a single liquid reward and mice were required to consume all six rewards in order to complete the task. Mice typically exhibit win-shift foraging behaviours, whereby they explore previously un-entered arms in favour of those already entered (Hyde, Hoplight, & Denenberg, 1998; Anagnostaras et al., 2003). Therefore, we hypothesised that wild type (WT) mice would quickly adopt a win-shift strategy and minimise the number of errors or return visits to previously depleted reward locations within a trial.

In order to characterise the effects of hippocampal (HPC) cell loss on the foraging, the first experiment examined the performance of male C57Bl/6 mice on the foraging task following excitotoxic lesions of the HPC (Experiment 1). We hypothesised that mice with hippocampal lesions would show increased working memory errors, i.e., return visits to depleted pots. In addition, based on evidence that rats with hippocampal damage displayed an increased tendency to return to previously visited locations (Whishaw & Tomie, 1997; Honey, Marshall, Mcgregor, Futter, & Good, 2007), we also hypothesised that lesioned mice would display perseverative behaviour by returning immediately to locations recently visited and depleted of reward.

Previous studies have shown that the contribution of the hippocampus to performance on the radial arm maze is related to the type of information (i.e., extramaze versus intra-maze cues) used to guide navigation. For example, Jarrard, Davidson, and Bowring (2004) showed that rats with hippocampal lesion had severe deficits in spatial working and reference memory components of an 8 arm radial maze but lesioned rats were capable of acquiring a non-spatial version of the task to control levels of performance (see also, Jarrard, 1983; M'Harzi & Jarrard, 1992). To test the hypothesis that mice with HPC lesions would be able to forage efficiently using intra-maze cues, Experiment 2 assessed foraging when distal visual extramaze cues were obscured, by drawing a black curtain around the arena, and each pot was identified by a unique pattern on its external wall.

Finally, Experiment 3 examined whether foraging behaviour was disrupted in PDAPP mice over the course of ageing. The development of synaptic pathology caused by the accumulation of β-amyloid peptide in the brain is thought to be a key initial event in the development of memory loss, supported by the medial temporal lobe. Dodart and colleagues tested this hypothesis in PDAPP mice using a radial arm maze procedure (Dodart et al., 1999). Using an uninterrupted 3/8 reference and working memory task, PDAPP mice were impaired on both reference and working memory components at 3, 6 and 10 months of age. However, the nature of this impairment and whether search strategies change with age in PDAPP mice remains unclear. More recently, Clark et al. (2015) showed that the performance of 3xTg mice may depend on task requirements in the radial arm maze. More specifically, 3xTg developed age-dependent and age-independent deficits in a 4 from 8-arm radial arm procedure. Performance of 3xTg mice on an uninterrupted version of the radial arm maze was normal at both 3 and 8 months of age. In contrast, retention of a 4-baited arm procedure, that included a delay between choices, was impaired at both 3 and 8 months of age in transgenic mice. The main aim of Experiment 3 was therefore to determine whether the accumulation of Aβ pathology caused an age-related change in search or foraging strategy and working memory errors in PDAPP mice. The pattern of locations visited and the type of error made by control and mutant mice was assessed (within-subjects) during ageing using an uninterrupted foraging procedure. Based on results from previous studies with PDAPP mice, it was hypothesised that transgenic mice would show both age-independent and age-dependent impairments in performance.

2. Methods

2.1. Subjects

For experiments 1 and 2 a total of 26 male C57Bl/6 mice aged 6 months were used to assess HPC involvement in the foraging task. Thirteen mice received bilateral HPC excitotoxic lesions and 13 received control (SHAM) surgery (as described below). Three weeks prior to behavioural assessment. However, due to insufficient hippocampal damage, 2 mice were removed from Experiment 1 and 2 analysis. Therefore, a final number of 13 SHAM control mice and 11 HPC lesion mice were used to assess the role of the HPC in the foraging task. Experiment 3 used a total of 29 mice; 14 heterozygous male PDAPP mice (Games, Adams, Wolozin, & Zhao, 1995) expressing the $hAPP^{V717F}$ genetic mutation and 15 wt littermate control mice (all maintained on a C57Bl/6 genetic background (Harlan) as previously described (Hartman et al., 2005). The same mice were tested at ages 6–8, 10–12 and 14–16 months of age to ascertain any age-dependent changes in performance in PDAPP mice.

All mice used throughout this study were housed in standard conditions in cages measuring L: 48 cm × W: 15 cm × H: 13 cm with an opaque plastic base and a wire top. The cage floors were covered in sawdust, approximately 1 cm deep, and contained a cardboard tube, wooden gnawing block and approved nesting material. Holding rooms were maintained at a stable temperature and relative humidity levels at around 21 °C ± 2 °C and 60 ± 10% respectively. Mice were given *ad libitum* access to food and water, unless otherwise stated as part of a behavioural test, and were kept on a 12hr light/dark cycle. All behavioural testing was carried out during the light hours. All animals were health-checked weekly and maintained according to UK Home Office and EU regulations and the Animal Scientific Procedures Act (1986).

2.2. Surgery

Mice were anaesthetised with Isoflurane [2-chloro-2- (difluromethoxy)-1, 1, 1-trifluoro- (ethane)] in O2 during stereotaxic surgery. The skull was exposed by a scalp incision. A bone flap was removed overlying the infusion sites in each hemisphere (see Table 1a). Infusions of 0.09 mM N-Methyl D-Aspartic Acid (NMDA, Sigma-Aldrich, UK) in sterile phosphate were delivered at a rate of 0.3 µl per minute into each hemisphere using a 30G cannulae microinjection 2 µl Hamilton #75 syringe (Hamilton Company, Reno, USA). Following each infusion, the needle was left in place for 2 min before being retracted slowly. Upon completion, the wound was sutured and the animal was given a subcutaneous injection of gluco-saline to aid rehydration. In SHAM-operated mice, 2 holes were drilled in accordance to the