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Tc1 mouse model of trisomy-21 dissociates properties of short- and long-term recognition memory

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ABSTRACT

The present study examined memory function in Tc1 mice, a transchromosomic model of Down syndrome (DS). Tc1 mice demonstrated an unusual delay-dependent deficit in recognition memory. More specifically, Tc1 mice showed intact immediate (30 sec), impaired short-term (10-min) and intact long-term (24-h) memory for objects. A similar pattern was observed for olfactory stimuli, confirming the generality of the pattern across sensory modalities. The specificity of the behavioural deficits in Tc1 mice was confirmed using APP overexpressing mice that showed the opposite pattern of object memory deficits. In contrast to object memory, Tc1 mice showed no deficit in either immediate or long-term memory for object-in-place information. Similarly, Tc1 mice showed no deficit in short-term memory for object-location information. The latter result indicates that Tc1 mice were able to detect and react to spatial novelty at the same delay interval that was sensitive to an object novelty recognition impairment. These results demonstrate (1) that novelty detection *per se* and (2) the encoding of visuo-spatial information was not disrupted in adult Tc1 mice. The authors conclude that the task specific nature of the short-term recognition memory deficit suggests that the trisomy of genes on human chromosome 21 in Tc1 mice impacts on (perirhinal) cortical systems supporting short-term object and olfactory recognition memory.

1. Introduction

Down syndrome (DS) is an aneuploidy syndrome caused by a trisomy of human chromosome 21 (Hsa21; Chapman & Hesketh, 2000). Approximately 95% of individuals with DS have 47 chromosomes as opposed to 46 that are present in the typical population. The remaining 5% of DS cases are caused by translocation, or partial trisomy (Desai, 1997). DS is the most common genetically defined cause of intellectual disability, with individuals experiencing cognitive impairments, including deficits in learning and memory (Silverman, 2007). Individuals with DS have an increased risk of developing early-onset Alzheimer's disease (AD), which is thought to reflect, at least in part, overexpression of the amyloid precursor protein (*APP*; Beyreuther et al., 1993). In order to understand the mechanism(s) by which trisomy of chromosome 21 impacts intellectual development and memory function, various mouse models of trisomy 21 have been developed (Ruparelia, Pearn, & Mobely, 2013). The Tc1 mouse is unique in that it is a transchromosomic line that carries a freely segregating and almost complete copy of human chromosome 21 (Wiseman, Alford, Tybulewicz, & Fisher, 2009). Consistent with the impact of Hsa21 trisomy in humans, Tc1 mice show reduced long-term potentiation (LTP) in the hippocampal dentate gyrus region (O'Doherty et al., 2005) and impaired performance on tasks such as object recognition memory. However, unlike individuals with DS, Tc1 mice are not trisomic for *APP* (Gribble et al., 2013) and thus they provide an opportunity to evaluate the contribution of chromosome 21 genes to cognition in the absence of APP-related brain changes.

Morice et al. (2008) reported that Tc1 mice displayed a deficit in object recognition memory following a delay of 10-min, but not following a 24-h delay; which supported the conclusion that Hsa21 expression impaired short- but not long-term memory. This finding is in broad agreement with evidence from individuals with DS where verbal short-term or working memory processes are

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impaired, with relative proficiency in visuo-spatial short-term memory tasks (Wang & Bellugi, 1994; but see Yang, Conners, & Merrill, 2014). However, it remains unclear whether the deficit in short-term memory in Tc1 mice extends to a different sensory modality and whether memory for the visuo-spatial attributes of objects is relatively proficient. The latter issue is relevant given evidence that Tc1 mice display aberrant hippocampal short-term, but not long-term, synaptic plasticity, abnormal hippocampal spine morphology, and sub-region changes in the connectivity of the DG-CA3 network that contributes to disruption of place-cell activity (O'Doherty et al., 2005; Witton et al., 2015). It is generally acknowledged that a major contribution of the hippocampus to recognition memory is processing object location and context information (Barker & Warburton, 2011). In contrast, there is relatively little evidence that the hippocampus contributes to short-term object memory (see Hammond, Tull, & Stackman, 2004). The evidence for aberrant hippocampal morphology, plasticity and coding of place information (Witton et al., 2015) would suggest that memory for the spatial organisation of objects will be disrupted in Tc1 mice (c.f., Burke et al., 2011; Lenck-Santini, Rivard, Muller, & Poucet, 2005). Therefore, the aim of this study was twofold: First, we examined immediate, short and long-term recognition memory in Tc1 mice for both visual and olfactory information. Second, we examined memory for object-place information to test the hypothesis that aberrant hippocampal function in Tc1 mice would disrupt memory for the spatial organisation of objects.

2. Materials and methods

2.1. Subjects

Male Tc1 mice and their age-matched wild type (WT) male litter mates were bred at the Francis Crick Institute, London, transferred to Cardiff University, with appropriate legal documentation, at ~2 months of age and tested at 4–7 months of age. The average weight of the animals was 35 g. Animals were kept on a 12-h light/dark cycle, and all testing was conducted during the light phase of the cycle. Animals were kept in a temperature and humidity controlled environment and were maintained on *ad libitum* access to food and water. Each cage was provided with environmental enrichment in the form of cardboard nesting tubes and wood chew sticks. Tc1 and WT litter mates were housed together in groups of 2–4 per cage. The Tc1 and WT mice used in these experiments were generated from the mating of C57BL/6Jx129S8 (F2) Tc1 females, with C57BL/6Jx129S8 (F1) males. The genotype of the mice was determined by polymerase chain reaction analysis on tissue samples taken from the mice at weaning. (Tc1-specific primers forward: 5′-GGTTTGAGGGAACA CAAAGCTTAACTCCCA-3′; reverse: 5′-ACAGAGCTACAGCCTCTGA CACTATGAACT-3′; control primers forward: 5′-TTACGTCCATCGTG GACAGCAT-3′; reverse: 5′-TGGGCTGGGTGTTAGTCTTAT-3′).

Three separate cohorts of animals were used in the current study. Experiment 1a was conducted with a cohort of 26 animals (12 WT and 13 Tc1 mice); Experiments 1b, 2a and 2b were conducted on a new cohort of 16 animals (8 WT and 8 Tc1). The interval between experiments was approximately one week. Experiment 3 was conducted on a new cohort of 24 animals (12 WT and 12 Tc1 mice).

Experiment 4, used 11 heterozygous male Tg2576 mice that expressed the "Swedish" amyloid precursor protein mutation ($HuAPP_{695}SWE$; driven by a hamster prion protein promoter; cf. Hsiao et al., 1996) together with 10 WT male litter mate control mice, maintained on a hybrid background of C57BL/6 x SJL. The genotype of the mice was determined by taking ear clips., The tissue was then analysed using polymerase chain reaction (Tg2576 specific primers: 1502: 5′-GTGGATAACCCCTCCCCCAGCCTAGAC CA- 3′; 1503B: 5′- CTGACCACTCGACCAGGTTCTGGGT-3′; 1501: 5′- AAGCGGCCAAAGCCTGGAGGGTGGAACA-3′). Transgenic and WT mice were tested at the age of 10–11 months, with an average weight of 28 g. This age range was selected because Tg2576 mice display robust memory deficits at this age point (Barnes, Hale, & Good, 2004). All Tg2576 and WT mice were housed individually, with environmental enrichment in the form of card board nesting tubes and wood chew sticks. Mice were housed individually because of male aggression and the need to maximise survival rates. We acknowledge that individual housing, albeit through necessity, may have an impact on the behavioural phenotype of Tg2576 and WT mice. Nevertheless, the cognitive phenotypes we have reported previously and in the present study are similar to other published reports with this mouse line.

All experiments were performed in accordance with the UK Animals (Scientific Procedures) Act (1986) and associated guidelines, as well as European Union directive 2010/63/EU. The programme of work was also approved by the local ethical review committee at Cardiff University, UK.

2.2. Apparatus

The apparatus used for all experiments was a large Perspex arena, 60 × 60 × 40 cm, with a pale grey floor and clear walls, which for the purpose of this experiment were covered with white paper. The box was placed on a square table at waist height. The apparatus was set up in a quiet and brightly lit (38 cd/m^2 at the arena surface) behavioural testing room. Exploration was recorded with an overhead camera. The camera input was used to monitor activity in the arena on a television monitor and each session was recorded using a Philips DVDR recorder.

The duration of object exploration throughout the trials was recorded manually with a stopwatch. All objects used were everyday objects made of non-porous materials. All objects were at least 10 cm high to avoid the mice climbing and sitting on the objects, and were all weighted so that they could not be displaced by the animals. Both the arena and the objects (including novel objects) were cleaned thoroughly with water and ethanol wipes in between each trial in order to prevent the use of odour cues, urine and excrement were also removed from the arena after each trial.

For the olfactory recognition experiment, odour cubes (Dale Air Ltd, UK) were used. Odour cubes were 5 × 5 × 5 cm and red in colour with holes placed in one surface. The scents used were strawberry, coconut, banana, lime, mint, ginger, cinnamon and coriander.

2.3. Experimental design

The week prior to testing, mice were handled for 5 min a day. For three days prior to testing, mice were placed in the behavioural test room in their home cages, for 30 min a day. Mice were also given one habituation session in which to freely explore the arena with no objects present for 10 min. Training commenced the following day. In order to provide comparability with Morice et al. (2008), the mice were presented with three objects (or odour cubes) during the sample and test trials. The sample stage comprised two 10-min sample phases, each separated by a 10-min interval (spent in the home cage located in the testing room). In all experiments, mice received a ten-min test phase following a delay interval. The order of presentation of experimental conditions, and the spatial location of objects was counterbalanced amongst mice in order to avoid order effects or spatial biases.

For each experiment, the dependent variable was the amount of time spent by the animals exploring objects. Object exploration was defined as the time spent attending to (actively sniffing or

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