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Genetic Differences in Response to Novelty and Spatial Memory Using a Two-Trial Recognition Task in Mice

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A two-trial memory task, based on a free-choice exploration paradigm in a Y-maze, was previously developed to study recognition processes in Sprague-Dawley rats. Because this paradigm avoids the use of electric shock or deprivation that may have nonspecific effects and does not require learning of a rule, it may be particularly useful for studying memory in mice. Four inbred strains (Balb/cByJ, DBA/2J, C57BL/6J, and SJL/J), an F1 hybrid (C57BL/6 × SJL/J), and one outbred strain (CD1) were used to validate this task in mice and to characterize a strain distribution in response to novelty and working memory. Exploration was measured with a short (2 min) intertrial interval (ITI) between acquisition and retrieval, while memory was examined with longer intervals (30 min, 1 h, and 2 h). A study of the time course of the response to novelty revealed varying degrees of preference and/or habituation to novelty among the different strains, with CD1 exhibiting a very high response to novelty and others showing lower (C57 × SJL hybrids) to complete absence (SJL) of exploration of novelty. Memory span, assessed with increasing ITIs, varied widely among strains from 30 min (C57 × SJL hybrids) to at least 2 h (C57 and BALB). Such demonstrated sensitivity to a wide range of behavioral phenotypes supports the use of this spatial memory task as an effective tool for the study of genetic influences on the response to novelty and recognition processes in mice. © 2000 Academic Press

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INTRODUCTION

Mouse strain differences in learning and memory ability are well documented. A wide variety of paradigms have been studied measuring a range of learning from complex to

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simple associative learning (for reviews, see Bovet, Bovet-Nitti, & Oliviero, 1969; Crawley, Belknap, Collins, Crabbe, Frankel, Henderson, Hitzemann, Maxsson, Miner, Silva, Wehner, Wynshaw-Boris, & Paylor, 1997; Wahlsten, 1972, 1978). However, interstrain comparisons of learning and memory abilities are potentially complicated by both host (genetic) and environmental (experimental parameters) factors that may significantly impact performance, while not pertaining directly to learning and memory constructs per se. Performance levels in a variety of learning and memory procedures may be influenced by motivation to explore novelty, attentional processes, and memory for acquired information (Gerlai et al., 1994). Specifically the use of appetitive or aversive stimuli can enhance differences in motivation or reactivity between strains that are difficult to dissociate from associative and mnemonic processes. Due to the increasing use of a broad range of mouse genetic backgrounds for investigating normal and disrupted behavior, establishing a paradigm that permits the evaluation of novelty exploration and memory independently and validating it across a variety of genetic backgrounds and procedural variables is particularly valuable.

A two-trial memory task in a Y-maze, based on a free-choice exploration paradigm, has been previously developed to study recognition processes in rats (Dellu, Mayo, Cherkaoui, Le Moal, & Simon, 1992; Dellu, Fauchey, Le Moal, & Simon, 1997). During the first trial (acquisition), the animal is allowed to visit two arms of a Y-maze, the third being blocked with a door. During the second trial (retrieval), the door is opened, and the animal has free access to all three arms. Discrimination of novelty versus familiarity can then be studied by comparing exploration of the three arms. Memory can be tested by evaluating the influence of various intertrial intervals (ITIs) on recognition performance. Because the three arms of the maze are identical, discrimination of novelty vs familiarity is based only on the different aspects of the environment that the animal can perceive from each of them. The "map" of the spatial environment from each of the visited arms must be compared with areas of this environment never seen before. These spatial representations as maps include both topological information, with representations of the connectivity of space and its overall arrangement, and metric information (angle and distance) (for review, see Poucet, 1993).

This task provides many advantages for mouse studies. First, this task does not involve the learning of a rule and thus enables specific testing of working memory. Factors that may particularly influence performance in mice such as motivational or emotional states generated by commonly used procedures such as food deprivation, water avoidance, or the use of an electric foot-shock are minimized. Second, since it is based on the rodents' natural tendency to explore novelty, this motivational component can be assessed first by the use of a short intertrial interval when the mnemonic demand is minimal. Once preferential exploration of novelty is established, the measure of memory can be evaluated with longer ITIs. Because retention does not last longer than a few hours, performance can be assessed several times in the same animals (i.e., 1 week later). Third, locomotor activity, recorded as the number of arm visits, can be evaluated. Importantly, the influence of locomotor activity on memory performance is limited in this procedure since the dependent measure is principally based on the choice between a novel place and familiar places. Finally, measurement of behavior is quick, precise, and entirely automated, permitting a detailed analysis of performance. This task has previously been shown to be a useful tool under several behavioral and pharmacological conditions in rats (Conrad, Galea, Kuroda, &

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