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# Impaired spatial working and reference memory in segmental trisomy (Ts65Dn) mice

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**Abstract**

To evaluate the cognitive phenotype of the segmental trisomy 16 (Ts65Dn) mouse, a model of Down Syndrome (DS, trisomy 21), we assessed spatial working and reference memory using a 12-arm radial maze (RAM). Ts65Dn mice made a greater number of reference memory errors across trials compared to control mice. Both genotypes showed improvement across trials, although improvement was slower in Ts65Dn mice. Ts65Dn mice also made a greater number of working memory errors on the RAM, and in contrast to control mice, did not improve across trials, always performing at near-chance levels. These results provide evidence for both spatial working and reference memory deficits in Ts65Dn mice, characteristics of cognitive dysfunction. © 1998 Elsevier Science B.V.

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Down syndrome (DS, trisomy 21) is associated with profound learning and memory deficits in humans, including deficits in verbal memory, as well as in both short-term and long-term spatial memory [2,8,9]. Unlike other genetic disorders involving single gene mutations, it has been difficult to develop a viable animal model for a comprehensive study of DS behavior. Because of the genetic homology between the distal end of MMU16 and the distal end of HSA21, the segmental Ts65Dn mouse offers an opportunity to investigate the behavioral genetics of DS in an experimental animal [3–5]. One of the first steps in these studies is to characterize behavioral abnormalities in Ts65Dn animals and to determine whether these deficits resemble those found in DS. Specifically, deficits in spatial learning and memory are commonly reported in DS patients [2]. Previous work with the Ts65Dn mouse has found impaired learning in the Morris water maze [8,11] and impaired spatial working memory on the radial-arm maze (RAM) [6]. In the present study, we have used the RAM to characterize further both spatial reference and spatial working memory in adult Ts65Dn mice.

Male segmental Ts65Dn mice, the generation of which has been described previously [4], and cuploid littermate control B6C3HF1 mice (11–12 months of age) were obtained from Jackson Laboratories (Bar Harbor, ME). Ts65Dn mice were from the same genetic background as control mice. Prior to behavioral testing, all mice were opthalmalogically screened via direct examination of the retina by slit lamp, and found to be free of retinal degeneration. Mice were tested on a 12-arm maze previously described [6]. Initial body weights were determined for all animals before behav-

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ioral testing. Animals were food restricted to 4 g of lab chow daily to maintain animals at ~85% of their initial body weight. Mice were shaped daily for 9 days on the experimental apparatus, during which the mice were placed in the RAM individually for 5 min. Food pellets were located in the food cups, on the arms, and in the central arena. The animals were allowed to explore the maze and consume the food pellets. Food pellets (Bioserve, Frenchtown, NJ) were gradually reduced in number until they were located solely on the ends of each arm. Beginning on day 10 (designated trial 1 in Fig. 1), animals were run in a variation of the free-choice procedure described previously to test for both spatial reference and working memory [6]. A random subset of six maze arms was chosen and baited with food while the other six arms were left unbaited. Each animal was placed in the central arena and allowed to visit arms until all six *baited* arms had been visited or 5 min had elapsed. Animals were tested for 15 trials (1 trial/day) and the *same* six randomly selected arms were left unbaited for all 15 trials. Working memory errors were defined as the number of *revisits* to any of the arms while reference errors were defined as the number of *initial* visits to the six *never-baited* arms. After each animal had finished 15 trials, they were tested for two additional sensory discrimination trials, as described in [6]. Spontaneous alternation was also tested using methods described previously [6]. The RAM was manipulated so that 9 of the 12 arms were closed off and the remaining three open arms were arranged in a T-formation. No food cups or food were present on the maze during testing.

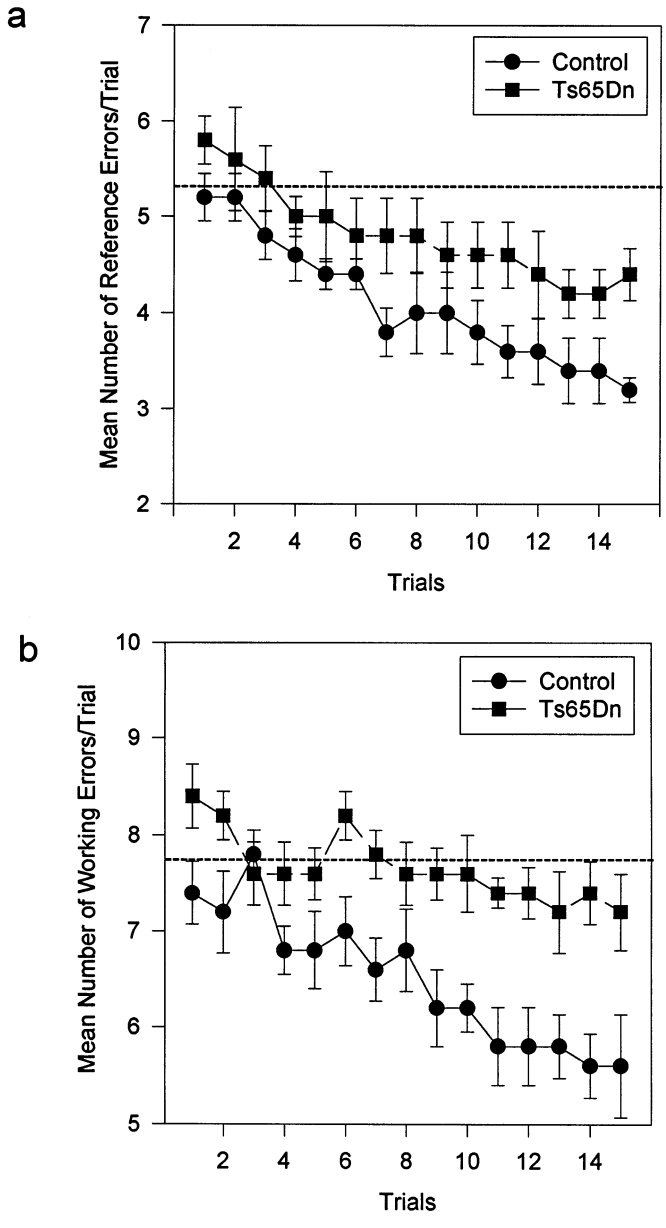


Fig. 1. Mean (±standard error of the mean (SEM)) choice accuracy of control and Ts65Dn mice on the 12-arm radial maze. The broken lines are modified estimates of chance performance that account for response bias. (a) Mean (±SEM) number of reference errors per trial. (b) Mean (±SEM) number of working errors per trial.

A modified estimate of chance performance was generated for use with statistical comparisons of the RAM data [1]. Briefly, the data for individual subjects were used to construct transition probability matrices that included the probability of moving from one arm to any other arm on the maze. The resulting probability matrices were used in Monte Carlo simulations. This estimate of chance, unlike a strict estimate which assumes random selection from all arms, is designed to take into account any systematicity in the arm-to-arm movement patterns (e.g. visiting adjacent arms in a clockwise fashion); thus, it provides a more stringent criterion for statistical analyses.

Ts65Dn mice displayed impaired spatial reference memory. Ts65Dn mice made a greater number of reference errors than did control animals ($P < 0.05$; mixed model ANOVA) (Fig. 1a). Initially (i.e. trial 1), Ts65Dn mice did not differ from control mice in the number of reference errors ($P > 0.05$). By trial 5, however, control mice were making fewer reference errors than Ts65Dn mice ($P < 0.05$). Both Ts65Dn and control mice made fewer errors across trials ($P < 0.05$ in both cases) (Fig. 1a) but the rate of learning was significantly lower among Ts65Dn (slope $= -0.16$) compared to control mice (slope $= -0.32$) ($P < 0.05$; Fig. 1a).

Ts65Dn mice also displayed impaired spatial working memory (Fig. 1b). Ts65Dn mice made a greater number of working errors compared to control animals ($P < 0.05$) (Fig. 1b). While the performance of control mice improved across trials ($P < 0.05$), Ts65Dn mice did not display a reduced number of working memory errors across trials ($P > 0.05$) and did not differ significantly from chance (Fig. 1b). There were no significant differences in spontaneous alternation between Ts65Dn and control mice (78% in both cases) ($P > 0.05$).

These data suggest that Ts65Dn mice have impaired spatial working memory, affecting their ability to process information regarding previously visited arms within each trial and avoiding revisits to these arms. These results are consistent with previous findings [6,7,11]. Ts65Dn mice also displayed significant deficits in spatial reference memory, choosing never-baited arms with greater frequency than control mice indicating an impaired ability to remember which arms were baited across trials. These data suggest that Ts65Dn mice, like DS individuals, have difficulty consolidating and/or retaining new memories [12].

These performance differences between control and Ts65Dn were not due to different response biases, an increased state of anxiety, sensorimotor deficits, or the use of perceptual cues (e.g. the sight or smell of food) to avoid visiting previously visited arms. Ts65Dn mice did not show heightened anxiety in the elevated plus maze [6]; they performed normally on a battery of sensorimotor tests including forelimb strength, turning ability, balance/coordination, motor or visual reflexes and olfactory ability [10] and there was no difference in behavior between control and Ts65Dn mice in the preference for baited versus unbaited arms. Because response bias is incorporated into the estimate of chance, choice accuracy in control animals does not reflect the use of a choice algorithm (e.g. always choosing adjacent arms) independent of memory that may be disrupted in Ts65Dn mice. In sum, Ts65Dn mice display deficits in both spatial working and reference memory analogous to those seen in DS individuals, that cannot be explained by other behavioral or sensorimotor anomalies. These findings may expand the applicability of the Ts65Dn mouse in studies of the physiological mechanisms underlying cognitive deficits in DS.

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