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Impaired Sustained Attention and Error-Induced Stereotypy in the Aged Ts65Dn Mouse: A Mouse Model of Down Syndrome and Alzheimer's Disease

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This study compared performance of 15- to 17-month-old Ts65Dn mice to that of littermate controls on an automated sustained attention task in which the location, onset time, and duration of brief visual cues varied unpredictably. Ts65Dn mice committed more omission errors than controls, particularly on trials with the briefest cues. Videotape data revealed that the trisomic mice attended less than controls during the period before cue presentation and engaged in stereotypic jumping and grooming immediately after making an error. These findings reveal that Ts65Dn mice are impaired in sustaining attention and exhibit heightened reactivity to committing an error, and support the validity of this mouse model for studying Down syndrome and Alzheimer's disease. The attention task, coupled with the videotape analyses of task performance, provides a useful paradigm for studying attention and reactivity to errors in mice.

Down syndrome (DS), a developmental disorder characterized by partial or full trisomy of chromosome 21, is the most common genetic cause of mental retardation. Children with DS exhibit a spectrum of cognitive deficits, including impaired language comprehension and production (e.g., Chapman & Hesketh, 2000; Vicari, Caselli, Gagliardi, Tonucci, & Volterra, 2002; Vicari, Caselli, & Tonucci, 2000); impaired short-term verbal memory (Jarrold, Baddeley, & Phillips, 2002; Kanno & Ikeda, 2002); and deficits in various executive functions, such as planning, inhibitory control, and shifting and sustaining attention (Brown et al., 2003; Munir, Cornish, & Wilding, 2000; Wilding, Cornish, & Munir, 2002). Stereotypic behavior also has been reported (Bodfish et al., 1995; Mitchell & Etches, 1977; Wieseler, Hanson, Chamberlain, & Thompson, 1988).

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Nearly all individuals with DS develop Alzheimer-like neuropathology early in life (20–30 years of age; e.g., K. E. Wisniewski, Wisniewski, & Wen, 1985), including neuritic plaques and neurofibrillary tangles (Shortridge, Vogel, & Burger, 1985; H. M. Wisniewski & Silverman, 1998); reduced cholinergic, noradrenergic, and serotonergic activity in the cortex and hippocampus (Godridge, Reynolds, Czudek, Calcutt, & Benton, 1987; Kish et al., 1990; Yates, Simpson, Maloney, Gordon, & Reid, 1980); and loss of basal forebrain cholinergic neurons (Casanova, Walker, Whitehouse, & Price, 1985; Sendera et al., 2000). Advances in understanding the pathogenic processes that lead to Alzheimer's disease (AD) suggest that the nearly universal incidence of early-onset AD in individuals with DS is likely due to overexpression of the gene on chromosome 21 that codes for the β-amyloid precursor protein (β-APP; Goldgaber, Lerman, McBride, Saffiotti, & Gajdusek, 1987; Isacson, Seo, Lin, Albeck, & Granholm, 2002; Tanzi et al., 1987). Accordingly, the cognitive impairments observed in adults with DS include not only those seen in children who have DS but also the impairments that characterize AD, including dementia (although dementia is not as universal as the neuropathology; e.g., Zigman, Schupf, Sersen, & Silverman, 1996).

Mouse models of DS are pivotal for elucidating the pathogenic process leading to brain damage in this syndrome. The Ts65Dn mouse, the most complete available animal model of DS to date, is trisomic for a segment of mouse chromosome 16 that is homologous to much of the long arm of human chromosome 21. This segment spans a region between the Ncam gene and the gene coding for APP to the myxovirus resistance-1 gene (Akeson et al., 2001; Davisson et al., 1993). The mice survive through adulthood and exhibit the low birth weight, muscular trembling, and craniofacial dysmorphology that are seen in human DS (Galdzicki,

Siarey, Pearce, Stoll, & Rapoport, 2001). Brain weight is normal during the early postnatal period, but Ts65Dn mice demonstrate a marked loss of basal forebrain cholinergic neurons, a reduction in nerve growth factor, increased expression of β-amyloid protein in the hippocampus, and astrocytic hypertrophy after 6 months of age (Granholm et al., 2002; Granholm, Sanders, & Crnic, 2000; Holtzman et al., 1995; Holtzman et al., 1996; Hunter, Bimonte-Nelson, Nelson, Eckman, & Granholm, 2004; Hunter, Isacson, et al., 2003; Sago et al., 1998). Although the increased APP expression observed in the segmentally trisomic mice (Holtzman et al., 1996; Hunter et al., 2004; Hunter, Isacson, et al., 2003; Reeves et al., 1995) is not accompanied by senile plaque deposition, even by 13–16 months of age (Holtzman et al., 1996; Reeves et al., 1995), mice have not been found to produce senile plaques unless they express human mutant APP (Wright et al., 1999).

Studies of Ts65Dn mice have uncovered general learning deficits (Reeves et al., 1995; Wenger, Schmidt, & Davisson, 2004) as well as a variety of impairments indicative of hippocampal dysfunction. For example, trisomic mice show reduced hippocampal long-term potentiation (Siarey, Stoll, Rapoport, & Galdzicki, 1997) and impaired memory function, both during early development (Demas, Nelson, Krueger, & Yarowsky, 1998; Dierssen et al., 2001; Escorihuela et al., 1995; Hyde & Crnic, 2001; Martinez-Cue et al., 2002) and in adulthood (Hunter, Bimonte, & Granholm, 2003; Hyde & Crnic, 2001). Although these phenotypic traits support the validity of the Ts65Dn mouse as a model for DS, no efforts have been made to date to test executive functions, which are known to be severely impaired in humans with DS, both early in life (Brown et al., 2003; Munir et al., 2000; Wilding et al., 2002) and after symptoms of AD begin to appear (Das, Divis, Alexander, Parrila, & Naglieri, 1995; Devenny, Krinsky-McHale, Sersen, & Silverman, 2000). The present study was designed to fill this gap by assessing sustained attention and reactivity to errors in these mice.

Method

Subjects

Thirty-four male mice (16 Ts65Dn mice and 18 wild-type controls) were bred in the University of Colorado Health Sciences Center (Denver, CO) from stock obtained from Jackson Laboratories (Bar Harbor, ME). The segmental trisomy must be maintained on a segregating genetic background whereby females positive for the extra segment of chromosome 16 are crossed to male F1 hybrids of C57BL6J/Ei and C3H/HeJ. Whenever possible, control and Ts65Dn mice selected for behavioral testing were littermate pairs. Before the mice were shipped to Cornell University for behavioral testing, they were typed for the presence of the extra chromosome by fluorescence *in situ* hybridization of blood smears using a bacterial artificial chromosome probe for the telomeric end of mouse chromosome 16 (Korenberg et al., 1999) at the Colorado Genetics Laboratory. DNA obtained from 1-mm tail clippings were typed by polymerase chain reaction amplification of the viral insert in the Pdeb6b gene that leads to retinal degeneration (Bowes et al., 1993). Mice homozygous for this mutation were excluded from the study.

On arrival at Cornell University, the mice were housed singly in polycarbonate cages, with food and water available ad libitum. The mice were housed individually because of previous observations that male mice of this strain, caged in pairs, are prone to fighting when reunited after being removed for testing (Crnic, 2004). The mice were administered an object recognition task at age 7–8 months (data not shown), after which they were placed on a 12:12-hr reversed light–dark cycle (lights on at 6:00 p.m.). Training for the series of visual attention tasks began at age 10 months; the sustained attention task described in the present report was administered at 15–17 months of age. All procedures in the current experiments were approved by the Institutional Animal Care and Use Committee at Cornell University, and adhere to the National Institutes of Health's (1986) *Guide for the Care and Use of Laboratory Animals*.

Diet

At 9 months of age, the mice were placed on a restricted diet to maintain motivation for food reward throughout daily test sessions of approximately 50–70 trials. The daily ration was gradually reduced and then maintained at a level that produced target weights at approximately 80% of their prerestriction weight. A target weight of 80% was selected because the animals were somewhat overweight prior to introduction of the food restriction regimen. The daily ration consisted of a combination of the reinforcement obtained in the automated chambers (liquefied AIN-76A sweetened purified chow; Bio-Serv, Frenchtown, NJ) and regular lab chow (ProLab 1000; Purina Mills, Richmond, IN). After each daily testing session, the number of calories obtained as reward was calculated and subtracted from the total daily ration. The remainder was fed as chow in each mouse's home cage immediately after the daily test session. If a mouse completed fewer than 50 trials per session for two to three consecutive sessions, the ration was reduced by intervals of 0.05 g daily, whereas the ration was increased by intervals of 0.05 g if a mouse lost weight for 3 consecutive days. Testing took place 5 days per week; on nontesting days, each mouse was given 0.4 ml of the liquid diet plus the remainder of the ration in chow in its home cage.

Testing Apparatus

The mice were tested individually in one of six automated Plexiglas chambers, each controlled by a PC and enclosed in an insulated, sound-attenuating chamber. The testing chambers were adapted from the nine-hole operant chambers recently developed to assess attention in mice (Humby, Laird, Davies, & Wilkinson, 1999; Marston, Spratt, & Kelly, 2001). The slightly curved rear wall contained five circular response ports, 1 cm in diameter, located 2 cm above the floor and 5 mm apart. A nose-poke into any of these ports constituted a response (or choice). Infrared photodiodes, positioned inside each port 0.5 cm from the opening, monitored responses to the port. Green 4 mA LEDs, one embedded on the back surface of each port, provided the discriminative visual cues. On the chamber wall opposite the response ports was an alcove (15 mm wide, 2 cm above the floor) containing the dipper (ENV0302M, MED Associates, East Fairfield, VT) that dispensed the liquid reward. Access to the dipper alcove was controlled by a thin metal door, which was activated by a motor located on the outside of the testing chamber. As with the ports, head entries into the alcove were monitored by infrared photodiodes. A nose-poke into this alcove port was required to initiate each trial. All automated events in the chamber (door opening, dipper movement, responses, etc.) were timed, controlled, and recorded by custom programs written in QBASIC. Each chamber was fitted with an exhaust system, which transported the air from each chamber directly to the room exhaust ventilator system at a rate of four complete air changes per minute.

Automated Testing

At 10 months of age, the animals began training on a series of visual discrimination and attention tasks. The entire test series, which took approximately 7 months to administer, is described below but, for the sake of brevity, results are included only for the visual discrimination task and Sustained Attention Task 2.

Training

The mice were first administered a four-stage task sequence designed to establish familiarity with the chambers and shape the general response sequence required for completion of each trial in subsequent tasks. In Stage 1, the alcove door remained open throughout the session, and each nose-poke into the dipper alcove triggered a 5-s presentation of food reward (a "dip"). In Stage 2, each dip was followed by the closing of the alcove door and a 5-s intertrial interval. Therefore, the mouse learned to remove its head from the alcove so that the door could close and reopen to allow access to the next reward. In Stage 3, the mouse learned the general series of events that would later constitute a trial: initiation of a trial at the dipper alcove (which, for the first time, did not in itself trigger reward presentation), followed by a nose-poke into any one of the five ports on the opposite wall of the chamber, and then retrieval of the reward at the dipper alcove. The final training stage (Stage 4) was implemented to minimize potential port biases. For each session, only one of the five ports was available, but the open port rotated across sessions until approximately equal experience was gained at all ports.

Five-Choice Visual Discrimination Task

In this task, one of the five port LEDs was illuminated on each trial; the mouse was rewarded for making a nose-poke into the illuminated port. The location of the visual cue was pseudorandomized across trials, such that the number of cue presentations in each port was equal for each daily session. A 2-s delay separated trial initiation and cue onset; this delay allowed time for the mouse to turn around and orient toward the ports before cue illumination. The LED remained illuminated until the mouse made a response or until 32 s had elapsed. All trials on which the mouse made an initiation poke into the dipper alcove (regardless of the outcome of the trial) were defined as *response trials*. Failures to initiate a trial within 60 s were termed *nontrials*; no cues were presented on these trials. A 5-s time-out period was imposed following an error or a nontrial. This time-out period was signaled by the illumination of a 3-W houselight on the ceiling of the chamber. Errors included responding to an incorrect response port after trial initiation, failing to respond to any response port following trial initiation, and making a nose-poke into any response port prior to cue onset. A 5-s intertrial interval separated adjacent trials. Each mouse remained on this task until it reached a criterion of 80% correct for two out of three consecutive sessions, each containing at least 50 response trials.

Visual Discrimination Tasks With Shortened Cue Duration

Six subsequent visual discrimination tasks were administered, all of which were identical to the previous task but with progressively shorter cue duration. These tasks were designed to establish stable performance and to prepare the mice for subsequent attention tasks. The cue durations were 10.0 s, 5.0 s, 2.0 s, 1.4 s, 1.2 s, and 0.8 s, and the mice received these durations for 3, 10, 10, 6, 6, and 6, sessions, respectively.

Sustained Attention Task 1

In this task, the visual cue occurred unpredictably after a delay of 0 s, 2 s, or 4 s (in addition to the 2-s turnaround time). The computer recorded a *premature response* if the mouse responded to a port before the onset of the cue. The delays were presented randomly, but the number of presentations for each combination of precue delay and each port was balanced across the session. The mice were tested on this task for 20 sessions.

Sustained Attention Task 2

In this task, the delay before cue onset and the duration of the cue were varied randomly across trials. Each combination of cue port (five), precue delay (three), and cue duration (three) was presented an approximately equal number of times in each session. The stimulus delays were the same as in the prior task; the cue durations varied among 0.8 s, 1.0 s, and 1.4 s. The mice were tested for 20 sessions on this task.

Videotaping Procedures

For each mouse, two sessions of Sustained Attention Task 2 were videotaped and then coded for various behaviors (described below). A period of approximately 2 months separated the initial 20 test sessions on Sustained Attention Task 2 and the two videotaped sessions, during which time the video-coding apparatus was developed and debugged (see below). During a portion of this interval, the mice were tested on a selective-attention task that was identical in concept to the sustained attention task but with the inclusion of unpredictable olfactory distracters (Moon, Driscoll, Crnic, & Strupp, 2003). After this task, the mice (now 17–19 months of age) were given two sessions on the sustained attention task prior to the two videotaped sessions, to serve as a refresher on the task.

Videotaping Apparatus

Each chamber was equipped with a wide-angle infrared video camera and infrared LED light source attached to the ceiling directly over the center of each testing chamber. The camera allowed full view of the mouse at all times. Each camera was connected to a separate VHS videotape recorder. To facilitate identification of session events during videotape coding (e.g., correctness of responses, location of visual cues, demarcation of the intertrial interval), an array of infrared LEDs was positioned outside the chamber within viewing range of the camera. The LEDs signaled the onset of each trial, initiation of the trial, location of the visual cue, correct responses, and time-outs.

Determination of Intra- and Interrater Reliability

The videotaped sessions were coded by two investigators who were blind to the animals' genotype. Both raters coded all sessions. Before coding the two sessions presented here, the coders practiced with other taped sessions until a high level of intra- and interrater reliability was obtained. Pearson correlation coefficients for all dependent measures were equal to or greater than .90 for the final practice session as well as for the sessions presented in this report.

Behavioral Measures and Rating Scales

The frequency and duration of four behaviors were quantified from the videotaped sessions: (a) *wall climbing*, (b) *grooming*, (c) *jumping*, and (d) *exploring* (defined below). Also coded was the location of the behavior (the side containing the response ports or the side containing the dipper) as well as the portion of the trial in which the behavior occurred (demarcated by the intertrial interval, initiation, cue presentation, and response). An additional measure, *attending*, was calculated from existing measures as the percentage of time between trial initiation and cue presentation (i.e., during the precue delay) that the animal spent exploring or wall climbing on the side of the chamber containing the response ports. Preliminary observations of sessions on camera (prior to videotaping) indicated that both exploring and wall climbing near the ports was indicative of attentive behavior, based on the fact that this behavior was associated with successful detection of the cue.

Statistical Analyses

Statistical analyses were conducted with SAS (Version 8.2; SAS Institute, Cary, NC) on a Cornell University mainframe computer. Performance measures were analyzed with a generalized linear mixed models procedure

(PROC GLIMMIX), a procedure for conducting repeated measures analyses of variance with non-normal data (Wolfinger & O'Connell, 1993). Means were calculated for each animal for each testing condition, defined by the following variables: stimulus delay (0 s, 2 s, or 4 s), stimulus duration (0.8 s, 1.0 s, or 1.4 s), outcome of the previous trial (correct or incorrect), and session block (1–4). The 20 sessions of the task were divided into four blocks of 5 sessions each. The analyses were conducted on these means. The models used for these analyses included the aforementioned variables, genotype (control or Ts65Dn), and all relevant higher order interactions. Latency measures were log transformed prior to analysis to normalize their distribution. Each plot includes the standard error bars for the least squares means. However, the appropriate standard error for the difference in means is a function of these mean standard errors and their covariance.

It was necessary to analyze some dependent measures using nonparametric techniques. This was the case for premature responses (defined below) and nontrials, because they occurred so rarely (i.e., less than once per session on average). For each of these measures, a mean was calculated for each mouse, with the numerator being the total number of occurrences and the denominator being the total number of trials. These rates were then analyzed using Wilcoxon rank-sum tests with genotype as the between-groups factor. Wilcoxon rank-sum tests were also used to analyze genotype differences for all but one of the dependent measures for the videotape data (mean exploring duration, mean grooming duration, mean wall climbing duration, and jumping frequency) due to extreme non-normality of the distributions. The only exception was percentage attending, which met distribution assumptions for the generalized linear mixed models procedure. Grooming and jumping during the intertrial interval were analyzed separately for trials following an error and trials following a correct response, based on preliminary observations that these behaviors increased dramatically following an error.

Results

Visual Discrimination Task

There were no significant genotype differences in the number of errors (premature responses, inaccurate responses, and omission errors) to criterion, $F(1, 33) = 0.52$, $p = .48$, or trials to criterion, $F(1, 33) = 2.79$, $p = .11$. Although a small subset of Ts65Dn mice required more sessions to learn the task than did controls, the available data suggested that this difference did not reflect group differences in learning rate but rather the fact that the Ts65Dn mice, on average, completed fewer trials per session than controls, $F(1, 33) = 7.58$, $p = .01$.

Sustained Attention Task 2

Main effects of task variables. Several variables produced significant and consistent effects for all outcome measures on the sustained attention task. Specifically, increasing the delay prior to cue presentation and decreasing the duration of the visual cue decreased percentage correct and increased the rate of omission errors (all ps $< .0001$). Increasing the delay before cue onset also increased the incidence of premature responses ($p < .0001$). For all error types, the rate of committing an error was significantly higher on trials that followed an error than on trials that followed a correct response (all ps $< .0001$). Finally, significant main effects of session block were uncovered for all error types (all ps $< .0001$), with performance improving across the four blocks of sessions (i.e., with increasing experience on the task).

Percent correct. Percent correct was calculated for each testing condition (defined by the task parameters; e.g., delay, duration, etc.) by dividing the number of correct trials in that condition by the total number of response trials in that condition and multiplying by 100. Percentage correct was lower for the Ts65Dn mice than for controls, $F(1, 30) = 8.08$, $p = .008$. In addition, as is shown in Figure 1A, there was an interaction between genotype and session block, $F(3, 1051) = 5.46$, $p = .001$. Although the Ts65Dn mice and controls did not differ significantly in the first block of sessions (Sessions 1–5), the controls performed significantly better than the Ts65Dn mice in Session Blocks 2, 3, and 4,

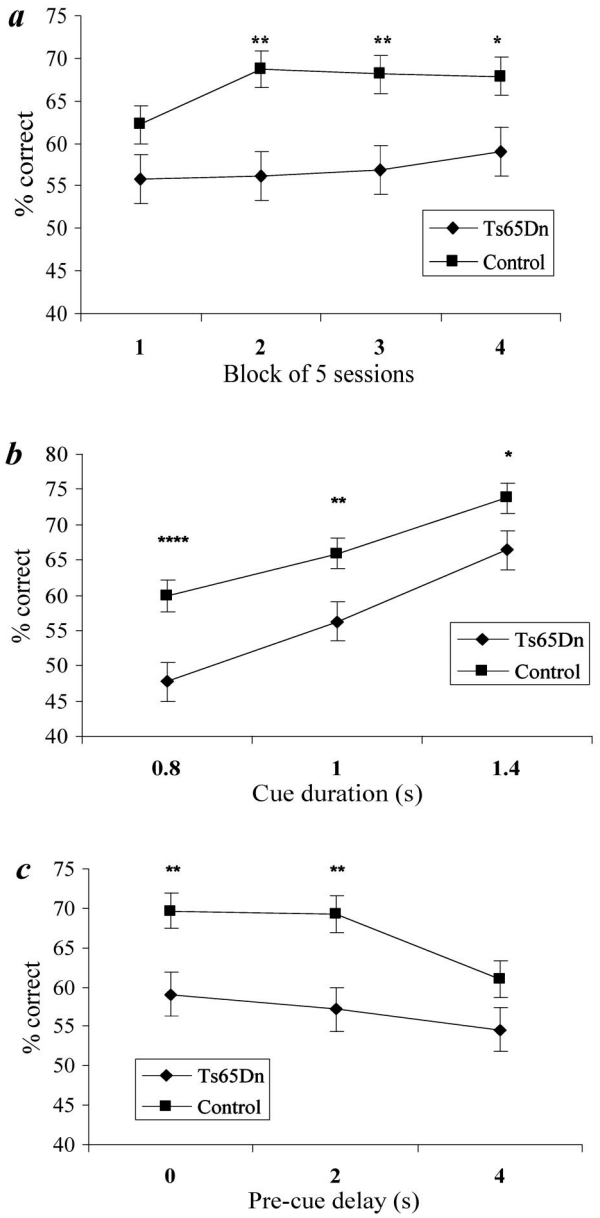

Figure 1. Percent correct of all response trials in Sustained Attention Task 2. A: Performance as a function of session blocks. *$p < .05$ and **$p < .01$ for Ts65Dn mice versus control mice. B: Performance as a function of cue duration. *$p < .05$, **$p < .01$, and ****$p < .0001$ for Ts65Dn mice versus control mice. C: Performance as a function of precue delay. **$p < .01$ for Ts65Dn mice versus control mice.

reflecting the fact that the controls improved more across the 20 sessions than did the Ts65Dn mice. In this regard, it is notable that the Ts65Dn mice completed fewer trials per session than controls, $F(1, 30) = 7.10$, $p = .01$, although the group difference was relatively small in magnitude (means for the controls and trisomic mice were 67.8 trials and 62.1 trials, respectively). The Genotype × Duration interaction was also significant, $F(2, 1051) = 2.44$, $p = .04$ (see Figure 1B). The controls performed significantly better than the Ts65Dn mice at all three durations (ps = .003, .01, and .03, for the 0.8 ms, 1.0 ms, and 1.4 ms cues, respectively), but group differences increased as the cue duration decreased. A significant interaction between genotype and delay was also found, $F(2, 1051) = 9.52$, $p < .0001$ (see Figure 1C). The Ts65Dn mice performed significantly less well than controls at the 0-s and 2-s delays, whereas they were only marginally worse than controls at the 4-s delay. As can be seen in Figure 1C, performance in the Ts65Dn mice was relatively constant across the three delays, whereas performance in the controls dropped at the longest delay.

Omission errors. An omission error was tallied if the mouse initiated a trial but then did not respond to any of the response ports within 5 s after cue onset. The Ts65Dn mice committed a higher percentage of omission errors than the control mice, $F(1, 27) = 10.04$, $p = .004$. There was also a significant Genotype × Session Block interaction, $F(3, 1050) = 6.25$, $p = .0003$, demonstrating that although the Ts65Dn subjects committed more omission errors than the controls at all session blocks, the genotype difference increased with increasing time on the task (see Figure 2). As was the case for percentage correct, this finding reflected greater improvement across the session blocks for the controls than for the trisomic mice.

Premature responses. *Premature responses* referred to trials in which the mouse made a nose-poke into one of the response ports prior to cue presentation. As noted above, premature responses were quite rare in this task, ranging from means of 0% to 15%. The Ts65Dn mice and controls did not differ on this measure $\chi^2(1, N = 34) = 0.13$, $p = .72$. Consistent with this comparison of the means, an examination of individual scores revealed that, of the 10 mice with the highest percentage premature responses, 5 were controls and 5 were Ts65Dn mice.

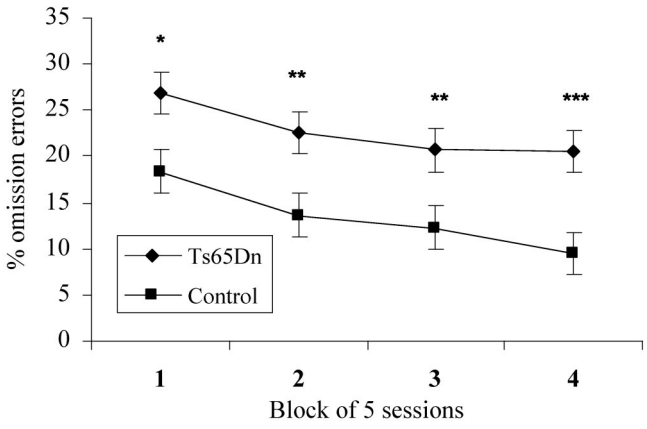

Figure 2. Percent omission errors of all response trials in Sustained Attention Task 2. *$p < .05$, **$p < .01$, and ***$p < .001$ for Ts65Dn mice versus control mice.

Nontrials. Nontrials were also quite infrequent, with averages for individual animals ranging from 0% to 13%. The Wilcoxon rank-sum test did not reveal genotype differences, $\chi^2(1, N = 34) = 0.12$, $p = .74$. Of the 10 mice that committed the highest percentages of nontrials, 5 were control and 5 were Ts65Dn.

Alcove latency. *Alcove latency* was defined as the latency to make a nose-poke into the alcove (dipper) port after it was raised (to initiate the next trial). Mean alcove latency was significantly longer for the Ts65Dn mice than for controls, $F(1, 33.8) = 7.59$, $p = .009$.

Response latency. Analysis of mean *response latency*, defined as the time between cue onset and a nose-poke into one of the response ports, revealed a significant main effect of genotype, $F(1, 33) = 5.24$, $p = .03$, and a significant Genotype × Session Block interaction, $F(3, 1019) = 14.28$, $p < .0001$. Whereas the groups did not differ in response latency in Block 1, the controls responded more quickly than the Ts65Dn mice in Session Blocks 2, 3, and 4 (ps = .03, .0008, and .04, respectively). In addition, genotype interacted with delay, $F(2, 1019) = 15.85$, $p < .0001$. The Ts65Dn mice were slower than controls at the 0-s and 2-s delays (ps = .008 and .008, respectively), but not at the 4-s delay ($p = .33$).

Dipper latency. *Dipper latency*, defined as the latency to retrieve the food reward following a correct response, decreased as the task progressed from Session Blocks 1 through 4, $F(3, 207) = 9.38$, $p < .0001$. Although the main effect of genotype was not significant, $F(1, 32.7) = 1.36$, $p = .25$, there was a significant Genotype × Session Block interaction, $F(3, 207) = 5.17$, $p = .002$. This interaction reflected the fact that although the dipper latency for both groups decreased across the four blocks, the latency for the trisomic mice decreased more quickly than controls. Dipper latency did not differ between the groups at either the first or last blocks, only during Block 3.

Analyses of the Videotape Data

During the 2 months that separated the initial 20 test sessions on Sustained Attention Task 2 and the two videotaped sessions, 3 Ts65Dn mice and 4 control mice died of natural causes, yielding 13 Ts65Dn mice and 14 control mice for the analyses described below.

Behaviors during the delay before cue onset. *Attending* was defined as the percentage of the delay period in which the mouse explored or wall climbed on the side of the chamber where the response ports were located. The Ts65Dn mice spent significantly less time attending than controls, $F(1, 14) = 8.02$, $p = .01$ (see Figure 3). The Ts65Dn mice also tended to spend more time grooming during the delay period than did controls, on both the port and dipper sides of the chamber (ps = .06 and .08, respectively). The groups did not differ on any other measures during the delay period.

Behaviors during the intertrial interval. The Ts65Dn mice jumped more than controls immediately following an error ($p = .01$), whereas the groups did not differ following a correct response ($p = .17$). As depicted in Figure 4, examination of data for individual mice revealed that 10 of the 13 Ts65Dn mice showed an increase in jump frequency on trials that followed an error relative to trials that followed a correct response, with some animals exhibiting a rather substantial increase in jump frequency. In

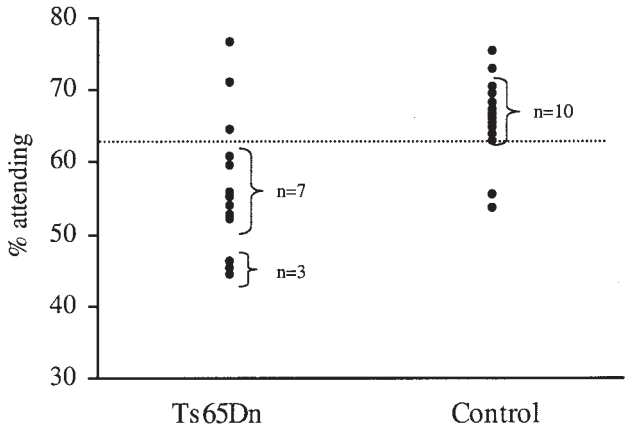

Figure 3. Percentage of precue delay spent attending to response ports during the two videotaped sessions of Sustained Attention Task 2. Each dot represents 1 mouse; line indicates overall mean attending score of 62%.

contrast, the jump rate for all control animals was very similar after an error versus after correct response, with most difference scores being very close to zero. An analysis of these difference scores (jump rate following an error minus jump rate following a correct response) revealed significant group differences ($p < .01$). Although the average increase in jump frequency per trial was relatively low for both groups, it is notable that a subset of the Ts65Dn mice exhibited bouts of forceful, repetitive jumping after committing an error. Committing an error also increased grooming during the intertrial interval for the trisomic mice but not the controls, with the result that the groups differed in grooming time following an error ($p = .004$) but not after a correct response ($p = .33$).

Because the videotape data were collected several months after administration of Sustained Attention Task 2, some age-related changes in performance were expected to occur, particularly for the Ts65Dn mice. A comparison of the automated performance data from the initial 20 sessions on Sustained Attention Task 2 with performance on this same task for the two videotaped sessions revealed that group differences were comparable at the two time points for all measures except alcove latency. For the videotaped sessions, there was a significant interaction between genotype and outcome of the previous trial for alcove latency, $F(1, 164) = 23.74$, $p < .0001$, an effect that was not seen earlier. At this latter time point, the groups did not differ in alcove latency for trials following a correct response, whereas the alcove latency following an error was much longer for the Ts65Dn mice than for controls ($p < .0001$). This statistical interaction reflected the fact that the controls made an alcove response (to initiate the next trial) much more quickly after an error than after a correct response. This pattern appears to be caused by increased grooming after a correct response relative to that seen following an error (*M*s = 3.3 s following an error vs. 1.8 s following a correct response), presumably because of the consumption of the liquid reward. In contrast, the alcove latency of the trisomic mice did not vary as a function of the previous trial outcome, being comparable in both conditions to the latency of controls following a correct response. The finding that alcove latency was longer for the trisomic mice than for controls after an error but not after a correct response accords with the videotape data, which revealed that the Ts65Dn mice jumped and groomed more than controls during intertrial intervals following an error, apparently also resulting in longer latencies to initiate the next trial.

Discussion

The present findings provide the first evidence for deficient sustained attention in the Ts65Dn mouse. This inference is based on both the performance measures and the videotape coding data. Percentage correct was lower for the Ts65Dn mice than for controls, particularly for the briefest visual cues, a pattern indicative of impaired attention. This performance deficit was primarily due to a much higher incidence of omission errors in the trisomic mice. The videotape coding analyses provided additional insight into the basis of this increased omission error rate. These data revealed that the Ts65Dn mice attended to the response ports less than controls in the period between trial initiation and cue presentation and therefore were more likely to miss the cue when it was presented. It is notable that this measure more clearly differentiated the two groups than did comparisons of mean performance level in the task. For example, an examination of the proportion of mice in each of the two groups that scored above the overall mean of 62% attending revealed that only 23% of the Ts65Dn mice scored above this level, in contrast to 86% of the controls. This impairment in sustained attention in the Ts65Dn mice supports the validity of this model of human DS and AD, as deficits in this domain have also been reported in children with DS (Brown et al., 2003; Tomporowski, Hayden, & Applegate, 1990; Wilding et al., 2002) and elderly individuals with DS, the latter being the most appropriate comparison group for the aged Ts65Dn mice in this study (Das et al., 1995; Das & Mishra, 1995). Finally, because attentional dysfunction contributes significantly to the functional impairment of humans with AD (Nebes & Brady, 1989; Parasuraman, Greenwood, Haxby, & Grady, 1992), demonstration of this type of dysfunction in adult Ts65Dn mice is important for establishing the validity of this mouse model, as most adults with DS exhibit AD (Zigman et al., 1996).

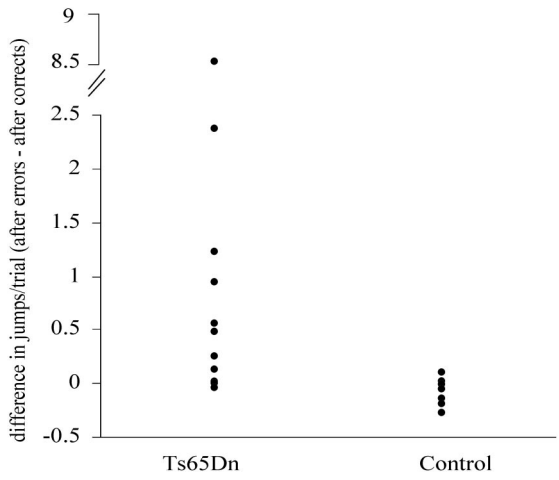

Figure 4. Difference scores reflecting the increase in jumping frequency (jumps per /trial) on trials following an error versus on trials following a correct response during the two videotaped sessions of Sustained Attention Task 2. Each dot represents 1 mouse.

The magnitude of group differences for several performance measures (percentage correct, accuracy, and omission errors) increased across the four session blocks of the sustained-attention task, due to fact that that the performance of the Ts65Dn mice plateaued at a lower level than did that of the controls. The basis of this lower plateau for the trisomic mice is not entirely clear. Decreased motivation in the Ts65Dn mice is not a likely explanation, as three measures of motivation—nontrial rate, dipper latency, and alcove latency following correct trials—did not differentiate the two groups. A deficit in associative learning cannot be excluded as a contributing factor, although a learning deficit would be expected to manifest as a slower rate of improvement but with a comparable level of asymptotic performance. This is not the pattern seen in the Ts65Dn mice: Despite having clearly mastered the basic rules of this series of attention tasks, as evidenced by performing well above chance, they failed to improve across the 4 weeks of daily testing on the sustained attention task. An impaired ability to benefit from experience on prior, related tasks (impaired transfer of learning), a defining feature of mental retardation syndromes (e.g., Strupp, Strupp, Bunsey, Levitsky, & Hamberger, 1994), is also a possible contributing factor, although here too one would expect this type of dysfunction to manifest as a slower learning rate with a comparable level of asymptotic performance. Rather, the lower asymptote of the trisomic mice more likely reflects their attentional dysfunction as well as the confusion or disorientation (i.e., dementia) that may be occurring in Ts65Dn animals of this age, commensurate with the development of AD-like neuropathology (Granholm et al., 2000; Holtzman et al., 1996; Hunter, Isacson, et al., 2003).

The Ts65Dn mice and controls also exhibited interesting differences in their reaction to committing an error. Performance of animals in both groups was significantly disrupted by committing an error: All types of errors increased on trials following an error, relative to trials that followed a correct response. Whereas this basic pattern was seen for both groups, the Ts65Dn mice appeared to be more disturbed following an error than did controls, as evidenced by bouts of intense stereotypic jumping and grooming during the intertrial interval following an error. Because these stereotypical behaviors were more frequent and intense on trials following an error than on trials following a correct response, they appear to reflect the stress of committing an error, failing to receive a food reward, or both. These findings are consistent with previous observations that Ts65Dn mice exhibit stereotypical behavior in their home cages and when stressed by rotorod testing or shock-motivated discrimination (Crnic & Pennington, 2000; Hyde, Crnic, Pollock, & Bickford, 2001; Turner et al., 2001). The present results extend these findings by demonstrating that stereotypical behavior can also be induced in these mice by committing an error, a common occurrence in the lives of individuals with DS and other mental retardation syndromes.

A comparison of the alcove latency data from the first 20 sessions of Sustained Attention Task 2 (when the mice were 15–17 months of age) with the data from the two videotaped sessions (when the mice were 17–19 months of age) suggests that the stress-induced stereotypy in the Ts65Dn mice became more pronounced with age. These age-related changes in error reactivity may reflect the coincident age-related degeneration of the cholinergic system that has been reported in Ts65Dn mice (Granholm et al., 2002; Granholm et al., 2000; Holtzman et al., 1995; Holtzman et al., 1996; Hunter et al., 2004; Hunter, Isacson, et al., 2003). The role of the cholinergic system in modulating error reactivity was previously demonstrated in our laboratory (Driscoll, Gardiner, Beaudin, & Strupp, 1999). It is also possible that the alterations in reactivity to errors in the Ts65Dn mice are due to pathology in other neurotransmitter systems that have been implicated in affect or arousal regulation (e.g., noradrenergic, dopaminergic, serotonergic) but that have been much less well studied in this mouse model. It is notable, however, that alterations in noradrenergic functioning have been observed in the cerebral cortex and hippocampus in Ts65Dn mice (Dierssen et al., 1997).

In contrast to these group differences in error-induced stereotypical behavior, the two groups did not differ in the extent to which an error disrupted task performance on the next trial. For both groups, committing an error increased the probability of an error on the next trial, to a comparable degree. However, the lack of group differences in this case may be unique to the characteristics of this task. In particular, the energetically demanding stereotypies exhibited by the Ts65Dn mice, which delayed the initiation of the next trial (discussed above), may have dissipated these animals' emotional reactions to committing an error. In contrast, it is likely that in everyday life, or in another type of task in which the trials are presented in quick succession, this exaggerated response to committing an error would disrupt task performance.

The stress-induced stereotypical behaviors seen in the Ts65Dn mice are reminiscent of the repetitive behaviors (e.g., body rocking and finger weaving) often seen in response to delays of reinforcement in humans with DS and other mental retardation syndromes (Wieseler et al., 1988). Stereotypical behaviors in humans with mental retardation, often including self-injurious behaviors, are viewed as a significant problem and are generally refractory to treatment (Branford, Bhaumik, & Naik, 1998; Miller & Jones, 1997; Willemsen-Swinkels, Buitelaar, Nijhof, & van England, 1995). Previous attempts to develop an animal model of this type of maladaptive behavior have been unsuccessful. The present demonstration of error-induced stereotypical behavior in Ts65Dn mice provides a model system for elucidating the neural mechanisms underlying these behaviors which, in turn, can inform efforts to develop effective pharmacological interventions.

Conclusions and Implications

The deficient sustained attention and stress-induced stereotypical behavior observed in the aged Ts65Dn mice parallels deficits in these same domains for aged individuals with DS and AD (Das et al., 1995; Wieseler et al., 1988), providing support for the validity of the Ts65Dn mouse as a model of DS and AD. These findings further delineate the cognitive profile of the Ts65Dn mouse, as previous reports focused on aspects of hippocampal function such as deficient working and reference memory (Bimonte-Nelson, Hunter, Nelson, & Granholm, 2003; Hunter, Bimonte, & Granholm, 2003; Martinez-Cue et al., 2002) and context discrimination learning (Hyde & Crnic, 2001; Hyde, Frisone, & Crnic, 2001) as well as object recognition (Hyde & Crnic, 2002). In addition, the demonstration of error-induced stereotypy in the Ts65Dn mouse will provide a valuable model system for studying the stereotypic behavior commonly seen in DS and other mental retardation syndromes (Bodfish et al., 1995; Rollings & Baumeister, 1981).

Future studies are needed to disentangle which of these observed effects are specific to aged Ts65Dn mice and which are also seen earlier in life, before the onset of AD-like neuropathology. These studies will need to include both aged and young Ts65Dn mice, the latter being less than 6 months of age, the approximate age at which AD-like neuropathology (Granholm et al., 2000; Holtzman et al., 1995) and cognitive decline (Hunter, Bimonte, & Granholm, 2003) begin to appear. Regardless of the age of onset of these deficits, the results from the current mouse cohort are in accordance with the findings from aging humans with DS, who exhibit AD-like neuropathology and dementia in addition to the cognitive impairments seen early in life (Das et al., 1995; Isacson et al., 2002).

Finally, the present sustained attention task, combined with the videotape analyses, provide novel tools for studying attention in mouse models. The dual unpredictability of cue onset time and cue duration provides a more sensitive index of sustained attention than does manipulation of only one of these variables, based on prior rat studies using comparable tasks (Morgan et al., 2001; Morgan et al., 2002). This dual manipulation has not previously been implemented in mouse attention tasks. In addition, the present results illustrate that pivotal information about group differences can be provided by videotape analysis of the animals while they are performing cognitive tasks. The videotapes uncovered important differences in attending behavior and stress-induced stereotypies that would have been missed by the automated-performance measures. Together, these tools constitute a novel behavioral phenotyping paradigm for mice with broad applicability.

References

Akeson, E. C., Lambert, J. P., Narayanswami, S., Gardiner, K., Bechtel, L. J., & Davisson, M. T. (2001). Ts65Dn—Localization of the translocation breakpoint and trisomic gene content in a mouse model for Down syndrome. *Cytogenetics and Cell Genetics, 93,* 270–276.

Bimonte-Nelson, H. A., Hunter, C. L., Nelson, M. E., & Granholm, A. C. (2003). Frontal cortex BDNF levels correlate with working memory in an animal model of Down syndrome. *Behavioural Brain Research, 139,* 47–57.

Bodfish, J. W., Crawford, T. W., Powell, S. B., Parker, D. E., Golden, R. N., & Lewis, M. H. (1995). Compulsions in adults with mental retardation: Prevalence, phenomenology, and comorbidity with stereotypy and self-injury. *American Journal of Mental Retardation, 100,* 183–192.

Bowes, C., Li, T., Frankel, W. N., Danciger, M., Coffin, J. M., Applebury, M. L., & Farber, D. B. (1993). Localization of a retroviral element within the rd gene coding for the beta subunit of cGMP phosphodiesterase. *Proceedings of the National Academy of Sciences, USA, 90,* 2955–2959.

Branford, D., Bhaumik, S., & Naik, B. (1998). Selective serotonin reuptake inhibitors for the treatment of perseverative and maladaptive behaviours of people with intellectual disability. *Journal of Intellectual Disability Research, 42,* 301–306.

Brown, J. H., Johnson, M. H., Paterson, S. J., Gilmore, R., Longhi, E., & Karmiloff-Smith, A. (2003). Spatial representation and attention in toddlers with Williams syndrome and Down syndrome. *Neuropsychologia, 41,* 1037–1046.

Casanova, M. F., Walker, L. C., Whitehouse, P. J., & Price, D. L. (1985). Abnormalities of the nucleus basalis in Down's syndrome. *Annals of Neurology, 18,* 310–313.

Chapman, R. S., & Hesketh, L. J. (2000). Behavioral phenotype of individuals with Down syndrome. *Mental Retardation and Developmental Disability Research Reviews, 6,* 84–95.

Crnic, L. S. (2004). [Cagemate aggression in male C57BL6J/C3H mice following brief separation]. Unpublished raw data.

Crnic, L. S., & Pennington, B. F. (2000). Down syndrome: Neuropsychology and animal models. *Progress in Infancy Research, 1,* 69–111.

Das, J. P., Divis, B., Alexander, J., Parrila, R. K., & Naglieri, J. A. (1995). Cognitive decline due to aging among persons with Down syndrome. *Research in Developmental Disabilities, 16,* 461–478.

Das, J. P., & Mishra, R. K. (1995). Assessment of cognitive decline associated with aging: A comparison of individuals with Down syndrome and other etiologies. *Research in Developmental Disabilities, 16,* 11–25.

Davisson, M. T., Schmidt, C., Reeves, R. H., Irving, N. G., Akeson, E. C., Harris, B., et al. (1993). Segmental trisomy as a model for Down syndrome. In C. J. Epstein (Ed.), *Phenotypic mapping of Down syndrome and other aneuploid conditions* (pp. 117–133). New York: Wiley-Liss.

Demas, G. E., Nelson, R. J., Krueger, B. K., & Yarowsky, P. J. (1998). Impaired spatial working and reference memory in segmental trisomy (Ts65Dn) mice. *Behavioural Brain Research, 90,* 199–201.

Devenny, D. A., Krinsky-McHale, S. J., Sersen, G., & Silverman, W. P. (2000). Sequence of cognitive decline in dementia in adults with Down's syndrome. *Journal of Intellectual Disability Research, 44,* 654–665.

Dierssen, M., Fillat, C., Crnic, L., Arbones, M., Florez, J., & Estivill, X. (2001). Murine models for Down syndrome. *Physiology & Behavior, 73,* 859–871.

Dierssen, M., Vallina, I. F., Baamonde, C., Garcia-Calatayud, S., Lumbreras, M. A., & Florez, J. (1997). Alterations of central noradrenergic transmission in Ts65Dn mouse, a model for Down syndrome. *Brain Research, 749,* 238–244.

Driscoll, L. L., Gardiner, S., Beaudin, S., & Strupp, B. J. (1999). Enduring effects of early lead exposure in a vigilance task: Contribution of cholinergic alterations. *Neurotoxicology and Teratology, 21,* 331.

Escorihuela, R. M., Fernandez-Teruel, A., Vallina, I. F., Baamonde, C., Lumbreras, M. A., Dierssen, M., et al. (1995). A behavioral assessment of Ts65Dn mice: A putative Down syndrome model. *Neuroscience Letters, 199,* 143–146.

Galdzicki, Z., Siarey, R., Pearce, R., Stoll, J., & Rapoport, S. I. (2001). On the cause of mental retardation in Down syndrome: Extrapolation from full and segmental trisomy 16 mouse models. *Brain Research Reviews, 35,* 115–145.

Godridge, H., Reynolds, G. P., Czudek, C., Calcutt, N. A., & Benton, M. (1987). Alzheimer-like neurotransmitter deficits in adult Down's syndrome brain tissue. *Journal of Neurology, Neurosurgery and Psychiatry, 50,* 775–778.

Goldgaber, D., Lerman, M. I., McBride, W. O., Saffiotti, U., & Gajdusek, D. C. (1987). Isolation, characterization, and chromosomal localization of human brain cDNA clones coding for the precursor of the amyloid of brain in Alzheimer's disease, Down's syndrome and aging. *Journal of Neural Transmission Supplement, 24,* 23–28.

Granholm, A. C., Ford, K. A., Hyde, L. A., Bimonte, H. A., Hunter, C. L., Nelson, M., et al. (2002). Estrogen restores cognition and cholinergic phenotype in an animal model of Down syndrome. *Physiology & Behavior, 77,* 371–385.

Granholm, A. C., Sanders, L. A., & Crnic, L. S. (2000). Loss of cholinergic phenotype in basal forebrain coincides with cognitive decline in a mouse model of Down's syndrome. *Experimental Neurology, 161,* 647–663.

Holtzman, D. M., Kilbridge, J., Chen, K. S., Rabin, J., Luche, R., Carlson, E., et al. (1995). Preliminary characterization of the central nervous system in partial trisomy 16 mice. *Progress in Clinical Biological Research, 393,* 227–240.

Holtzman, D. M., Santucci, D., Kilbridge, J., Chua-Couzens, J., Fontana, D. J., Daniels, S. E., et al. (1996). Developmental abnormalities and

age-related neurodegeneration in a mouse model of Down syndrome. *Proceedings of the National Academy of Sciences, USA, 93,* 13333–13338.

Humby, T., Laird, F. M., Davies, W., & Wilkinson, L. S. (1999). Visuospatial attentional functioning in mice: Interactions between cholinergic manipulations and genotype. *European Journal of Neuroscience, 11,* 2813–2823.

Hunter, C. L., Bimonte, H. A., & Granholm, A. C. (2003). Behavioral comparison of 4 and 6 month-old Ts65Dn mice: Age-related impairments in working and reference memory. *Behavioural Brain Research, 138,* 121–131.

Hunter, C. L., Bimonte-Nelson, H. A., Nelson, M., Eckman, C. B., & Granholm, A. C. (2004). Behavioral and neurobiological markers of Alzheimer's disease in Ts65Dn mice: Effects of estrogen. *Neurobiology of Aging, 25,* 873–884.

Hunter, C. L., Isacson, O., Nelson, M., Bimonte-Nelson, H., Seo, H., Lin, L., et al. (2003). Regional alterations in amyloid precursor protein and nerve growth factor across age in a mouse model of Down's syndrome. *Neuroscience Research, 45,* 437–445.

Hyde, L. A., & Crnic, L. S. (2001). Age-related deficits in context discrimination learning in Ts65Dn mice that model Down syndrome and Alzheimer's disease. *Behavioral Neuroscience, 115,* 1239–1246.

Hyde, L. A., & Crnic, L. S. (2002). Reactivity to object and spatial novelty is normal in older Ts65Dn mice that model Down syndrome and Alzheimer's disease. *Brain Research, 945,* 26–30.

Hyde, L. A., Crnic, L. S., Pollock, A., & Bickford, P. C. (2001). Motor learning in Ts65Dn mice, a model for Down syndrome. *Developmental Psychobiology, 38,* 33–45.

Hyde, L. A., Frisone, D. F., & Crnic, L. S. (2001). Ts65Dn mice, a model for Down syndrome, have deficits in context discrimination learning suggesting impaired hippocampal function. *Behavioral Brain Research, 118,* 53–60.

Isacson, O., Seo, H., Lin, L., Albeck, D., & Granholm, A. C. (2002). Alzheimer's disease and Down's syndrome: Roles of APP, trophic factors and ACh. *Trends in Neurosciences, 25,* 79–84.

Jarrold, C., Baddeley, A. D., & Phillips, C. E. (2002). Verbal short-term memory in Down syndrome: A problem of memory, audition, or speech? *Journal of Speech Language and Hearing Research, 45,* 531–544.

Kanno, K., & Ikeda, Y. (2002). Word-length effect in verbal short-term memory in individuals with Down's syndrome. *Journal of Intellectual Disability Research, 46,* 613–618.

Kish, S. J., DiStefano, L. M., Dozic, S., Robitaille, Y., Rajput, A., Deck, J. H., et al. (1990). [3H]vesamicol binding in human brain cholinergic deficiency disorders. *Neuroscience Letters, 117,* 347–352.

Korenberg, J. R., Chen, X. N., Devon, K. L., Noya, D., Oster-Granite, M. L., & Birren, B. W. (1999). Mouse molecular cytogenetic resource: 157 BACs link the chromosomal and genetic maps. *Genome Research, 9,* 514–523.

Marston, H. M., Spratt, C., & Kelly, J. S. (2001). Phenotyping complex behaviours: Assessment of circadian control and 5-choice serial reaction learning in the mouse. *Behavioural Brain Research, 125,* 189–193.

Martinez-Cue, C., Baamonde, C., Lumbreras, M., Paz, J., Davisson, M., Schmidt, C., et al. (2002). Differential effects of environmental enrichment on behavior and learning of male and female Ts65Dn mice, a model for Down syndrome. *Behavioural Brain Research, 134,* 185.

Miller, B. Y., & Jones, R. S. (1997). Reducing stereotyped behaviour: A comparison of two methods of programming differential reinforcement. *British Journal of Clinical Psychology, 36,* 297–302.

Mitchell, R., & Etches, P. (1977). Rhythmic habit patterns (stereotypies). *Developmental Medicine and Child Neurology, 19,* 545–550.

Moon, J., Driscoll, L. L., Crnic, L. S., & Strupp, B. J. (2003). Assessment of selective attention and error reactivity in aged Ts65Dn mice: A mouse model of Down syndrome (DS) and Alzheimer disease (AD). Program No. 114.21, *2003 Abstract Viewer and Itinerary Planner* [CD-ROM]. Washington, DC: Society for Neuroscience.

Morgan, R. E., Garavan, H., Smith, E. G., Driscoll, L. L., Levitsky, D. A., & Strupp, B. J. (2001). Early lead exposure produces lasting changes in sustained attention, response initiation, and reactivity to errors. *Neurotoxicology and Teratology, 23,* 519–531.

Morgan, R. E., Garavan, H. P., Mactutus, C. F., Levitsky, D. A., Booze, R. M., & Strupp, B. J. (2002). Enduring effects of prenatal cocaine exposure on attention and reaction to errors. *Behavioral Neuroscience, 116,* 624–633.

Munir, F., Cornish, K. M., & Wilding, J. (2000). A neuropsychological profile of attention deficits in young males with fragile X syndrome. *Neuropsychologia, 38,* 1261–1270.

National Institutes of Health. (1986). *Guide for the care and use of laboratory animals* (DHEW Publication No. 86-23). Washington, DC: U.S. Government Printing Office.

Nebes, R. D., & Brady, C. B. (1989). Focused and divided attention in Alzheimer's disease. *Cortex, 25,* 305–315.

Parasuraman, R., Greenwood, P. M., Haxby, J. V., & Grady, C. L. (1992). Visuospatial attention in dementia of the Alzheimer type. *Brain, 115,* 711–733.

Reeves, R. H., Irving, N. G., Moran, T. H., Wohn, A., Kitt, C., Sisodia, S. S., et al. (1995). A mouse model for Down syndrome exhibits learning and behaviour deficits. *Nature Genetics, 11,* 177–184.

Rollings, J. P., & Baumeister, A. A. (1981). Stimulus control of stereotypic responding: Effects on target and collateral behavior. *American Journal of Mental Deficiencies, 86,* 67–77.

Sago, H., Carlson, E. J., Smith, D. J., Kilbridge, J., Rubin, E. M., Mobley, W. C., et al. (1998). Ts1Cje, a partial trisomy 16 mouse model for Down syndrome, exhibits learning and behavioral abnormalities. *Proceedings of the National Academy of Sciences, USA, 95,* 6256–6261.

Sendera, T. J., Ma, S. Y., Jaffar, S., Kozlowski, P. B., Kordower, J. H., Mawal, Y., et al. (2000). Reduction in TrkA-immunoreactive neurons is not associated with an overexpression of galaninergic fibers within the nucleus basalis in Down's syndrome. *Journal of Neurochemistry, 74,* 1185–1196.

Shortridge, B. A., Vogel, F. S., & Burger, P. C. (1985). Topographic relationship between neurofibrillary change and acetylcholinesterase rich neurons in the upper brain stem of patients with senile dementia of the Alzheimer's type and Down's syndrome. *Clinical Neuropathology, 4,* 227–237.

Siarey, R. J., Stoll, J., Rapoport, S. I., & Galdzicki, Z. (1997). Altered long-term potentiation in the young and old Ts65Dn mouse, a model for Down syndrome. *Neuropharmacology, 36,* 1549–1554.

Strupp, B. J., Strupp, B. J., Bunsey, M., Levitsky, D. A., & Hamberger, K. (1994). Deficient cumulative learning: An animal model of retarded cognitive development. *Neurotoxicology and Teratology, 16,* 71–79.

Tanzi, R. E., Gusella, J. F., Watkins, P. C., Bruns, G. A., George-Hyslop, P., Van Keuren, M. L., et al. (1987, February 20). Amyloid beta protein gene: cDNA, mRNA distribution, and genetic linkage near the Alzheimer locus. *Science, 235,* 880–884.

Tomporowski, P. D., Hayden, A. M., & Applegate, B. (1990). Effects of background event rate on sustained attention of mentally retarded and nonretarded adults. *American Journal of Mental Retardation, 94,* 499–508.

Turner, C. A., Presti, M. F., Newman, H. A., Bugenhagen, P., Crnic, L., & Lewis, M. H. (2001). Spontaneous stereotypy in an animal model of Down syndrome: Ts65Dn mice. *Behavioral Genetics, 31,* 393–400.

Vicari, S., Caselli, M. C., Gagliardi, C., Tonucci, F., & Volterra, V. (2002). Language acquisition in special populations: A comparison between Down and Williams syndromes. *Neuropsychologia, 40,* 2461–2470.

Vicari, S., Caselli, M. C., & Tonucci, F. (2000). Asynchrony of lexical and morphosyntactic development in children with Down syndrome. *Neuropsychologia, 38,* 634–644.

Wenger, G. R., Schmidt, C., & Davisson, M. T. (2004). Operant conditioning in the Ts65Dn mouse: Learning. *Behavioral Genetics, 34,* 105–119.

Wieseler, N. A., Hanson, R. H., Chamberlain, T. P., & Thompson, T. (1988). Stereotypic behavior of mentally retarded adults adjunctive to a positive reinforcement schedule. *Research in Developmental Disabilities, 9,* 393–403.

Wilding, J., Cornish, K., & Munir, F. (2002). Further delineation of the executive deficit in males with fragile-X syndrome. *Neuropsychologia, 40,* 1343–1349.

Willemsen-Swinkels, S. H., Buitelaar, J. K., Nijhof, G. J., & van England, H. (1995). Failure of naltrexone hydrochloride to reduce self-injurious and autistic behavior in mentally retarded adults. Double-blind placebo-controlled studies. *Archives of General Psychiatry, 52,* 766–773.

Wisniewski, H. M., & Silverman, W. (1998). Aging and dementia of the Alzheimer type in persons with mental retardation. *Advances in Experimental and Medical Biology, 446,* 223–225.

Wisniewski, K. E., Wisniewski, H. M., & Wen, G. Y. (1985). Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Annals of Neurology, 17,* 278–282.

Wolfinger, R., & O'Connell, M. (1993). Generalized linear mixed models: A pseudo-likelihood approach. *Journal of Statistical Computing Simulations, 48,* 233–243.

Wright, K. L., Morgan, D. G., Yu, X., Goss, J. R., Salbaum, J. M., Duff, K., et al. (1999). Mice transgenic for a human amyloid precursor protein promoter-lacZ reporter construct. *Journal of Molecular Neuroscience, 13,* 111–120.

Yates, C. M., Simpson, J., Maloney, A. F., Gordon, A., & Reid, A. H. (1980). Alzheimer-like cholinergic deficiency in Down syndrome. *The Lancet, 2,* 979.

Zigman, W. B., Schupf, N., Sersen, E., & Silverman, W. (1996). Prevalence of dementia in adults with and without Down syndrome. *American Journal of Mental Retardation, 100,* 403–412.

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