

Sustained Attention in the Mouse: A Study of the Relationship With the Cerebellum

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To explore the role of the cerebellum in sustained attention, the authors tested *lurcher*, wildtype, and *lurcher* chimeric mice with zero, normal, and variable numbers of Purkinje cells, respectively, in a previously validated task of sustained attention. Results indicate that *lurcher* mice had a deficit in performance likely related to their motor disability, whereas *lurcher* chimeras performed similarly to wildtype controls. Presentation of auditory or visual distracters caused deficits in the performance of all mice that were specific to either signal (auditory) or nonsignal (visual) events. The authors' results do not support a role of the cerebellum in sustained attention, instead indicating that behavioral changes are an indirect result of motor deficits.

Keywords: vigilance, Purkinje, *lurcher*, chimera, motor

Several recent clinical studies have indicated a role for the cerebellum in attention (Allen, Buxton, Wong, & Courchesne, 1997; Casey et al., 2000; Corbetta et al., 1998; Coull, Frackowiak, & Frith, 1998; Le, Pardo, & Hu, 1998; Rees, Frackowiak, & Frith, 1997). However these findings lack support from an animal model system. In this study, the role of the cerebellum in sustained attention was assessed in a mouse model of Purkinje cell loss, the sole output from cerebellar cortex. To date, there have been few attempts at studying attention in mice (Bushnell, 1998), and to our knowledge, sustained attention has never before been tested in mice. We tested *lurcher* (*Lc/+*), wildtype (*+/+*), and *Lc/+–/+* chimeric mice in a task designed to measure sustained attention. *Lc/+* mice lose 100% of their Purkinje cells and develop severe ataxia consequent to a mutation in the $\delta 2$ glutamate receptor gene (Caddy & Biscoe, 1979; Zuo et al., 1997). *Lc/+* embryos combined with *+/+* embryos result in chimeric mice with variable numbers of Purkinje cells that do not develop ataxia, thereby providing an appropriate model to study cerebellar function (Martin, Escher, Goldowitz, & Mittleman, 2004; Martin, Goldowitz, & Mittleman, 2003).

Method

Subjects

The original stock of *Lc/+* mice, B6CBACaA^{w–j}/A-Grid2^{Lc}, was obtained from the Jackson Laboratory (Bar Harbor, Maine) and was main-

tained at the University of Tennessee Animal Care Facility and the University of Memphis Animal Care Facility. A total of 24 mice were tested in the sustained attention task (*+/+* controls, $n = 9$; *Lc/+–/+* chimeras, $n = 9$; *Lc/+*, $n = 6$). On the basis of previous results (Martin et al., 2004), we reasoned that *+/+* and *Lc/+* mice derived solely from the chimera production process would be acceptable, respectively, as wildtype and mutant control mice. Because the genotype of the mice was unknown until the histology was performed, litters were not culled to balance litter size. In addition, whenever possible, litters were raised in batches of two to three; as a result, the exact number of pups from each litter was unknown. However, litters tended to be large (seven or more pups) and included mice from all three genotypes.

Production of Aggregation Chimeras

Aggregation chimeras were made by the standard method of fusing two four- to eight-cell embryos and transplanting them into pseudopregnant ICR host female chimeras (Goldowitz, Moran, & Wetts, 1992). All surgical procedures and animal care were in accordance with National Institutes of Health guidelines for animal welfare.

Apparatus

All behavioral testing was done in 12 identical operant chambers (Model ENV-307; 15.9 cm long, 14 cm wide, 12.7 cm tall; Med Associates, St. Albans, Vermont). Each was equipped with two retractable response levers (Model E23-07) positioned to the left and right of the food magazine, a white stimulus light above the food magazine, and a houselight on the opposite side of the chamber. The specifications of these testing chambers are described elsewhere (Martin et al., 2004).

Procedure

Mice were initially food deprived to between 80% and 85% of their baseline body weight, habituated to the apparatus, and then trained to lever press for food reward in two stages: (a) Mice were trained to nose poke into the food magazine to consume the liquid reinforcement, and (b) mice were trained to press one of the two response levers to receive the liquid reward.

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Following successful lever-press training, mice entered into training for the sustained attention task.

The procedure for the sustained attention task was essentially the same as described in McGaughy and Sarter's (1995) study, with the exception of the signal durations (see below). We trained mice to discriminate between signal and nonsignal events using a stimulus light. Two seconds following each signal or nonsignal event, two response levers were extended into the chamber for 4 s or until a lever press occurred. Mice were reinforced following a signal event by pressing the left response lever (recorded as a hit) and following a nonsignal event by pressing the right response lever (recorded as a correct rejection). An incorrect response to a signal event was recorded as a miss, and an incorrect response to a nonsignal event was recorded as a false alarm. Each session involved a total of 144 trials that were pseudorandomly presented to ensure an equal number of signal and nonsignal trials.

During testing, each signal event lasted 50, 75, 100, or 500 ms with an intertrial interval (ITI) of 12 ± 3 s. Each signal duration was presented 18 times in a session so that there were 72 signal and 72 nonsignal events that occurred in a pseudorandom sequence. After mice correctly responded to $\geq 59\%$ of both the nonsignal events and the 500-ms signal events in which a response was made, for at least three of five consecutive sessions, mice moved into the first of five variations of the test program.

The only change during the first test variation was the illumination of the darkened chambers with the houselight. For the second variation, all parameters remained the same except that the ITI changed from 12 ± 3 s to 9 ± 3 s. During the third test variation, the houselight flashed at 0.5 Hz to create a visual distraction. In the fourth variation, the houselight returned to constant illumination, but an audio distraction was generated through the delivery of 80 dB white noise beginning 200 ms before a signal or nonsignal event. For the final test variation, the houselight was programmed to flash at three different frequencies: 0.5 Hz, 1 Hz, and 2 Hz, across three blocks of 24 signal and nonsignal events. The order of the houselight frequencies varied across sessions until all sequences were used (six sessions).

Histology

Following the completion of testing, we sacrificed mice and histologically prepared brain sections using previously described methods (Martin et al., 2003). We used immunocytochemistry with an anti-Calbindin antibody (Chemicon) to identify Purkinje cells.

Purkinje Cell Counts

Purkinje cell nuclei in every 50th section throughout the entire sagittal cerebellum were counted with the exception of the parafloccular lobe. We then estimated total numbers of Purkinje cells for the entire cerebellum from this sampling and corrected for split nuclei using the Abercrombie correction factor (Abercrombie, 1946). We previously found $+/+$ mice to consistently have more than 135,000 Purkinje cells. Thus, chimeric mice with over 135,000 Purkinje cells were designated as $+/+$ controls (Martin et al., 2003).

Data Collection and Statistical Analysis

The relative number of correct rejections [correct rejections/(correct rejections + false alarms)] and the relative number of hits [hits/(hits + misses)] at each signal duration were calculated for every test session. As signal and nonsignal events were presented in a pseudorandom sequence, there was no relationship between the presentation of nonsignal events and the four signal durations. To check for a response lever bias, we calculated a side-bias index (SB) using the following formula: $SB = (\text{hits} + \text{false alarms}) / (\text{hits} + \text{false alarms} + \text{misses} + \text{correct rejections})$. The values of SB varied between 0, which indicated only right response lever presses,

and 1, which indicated only left response lever presses (McGaughy & Sarter, 1995).

We analyzed results from the last nine sessions of each test using mixed-model analyses of variance (ANOVAs) with group as a between-subjects factor, and signal duration (four levels), session (nine levels), test variation (two or three levels), and houselight frequency (three levels) as within-subjects factors when appropriate. When any ANOVA indicated a significant interaction, simple main effects tests were conducted. Additionally, when appropriate, we made comparisons using Dunnett's *t* tests.

A second set of analyses was conducted to determine potential relationships between the total number of cerebellar Purkinje cells and the dependent measures relative hits and relative correct rejections from each test variation. In these analyses, the average of these dependent measures across the final nine test sessions of each variation was used together with the total Purkinje cell number from each mouse in the group of chimeric mice and in all three groups combined to calculate Pearson product-moment correlations. The two-tailed alpha level was set to $p < .05$ for these correlations.

Results

Of a group of 51 mice that originally began training for the sustained attention task, only 24 mice completed testing. Of the remaining 27 mice, most of the mice failed to advance past the training phase of the task following over 4 months of training. Histological assessment revealed that the 27 mice that failed to complete the task comprised *Lc/+*, chimeric, and $+/+$ mice, although a disproportionate number were *Lc/+* mice ($n = 13$). Of the 24 mice that completed testing, 6 were *Lc/+*, having no Purkinje cells; 9 were *Lc/+*- $+/+$ chimeras, with total Purkinje cell numbers ranging from 18,000 to 125,000; and 9 were $+/+$ and possessed more than 135,000 Purkinje cells (see Figure 1).

The Effect of Background Light on Test Performance

Analyses were done comparing the last 3 days of testing with the houselight off to the first 3 days with the houselight on for a subset of 14 mice in which data were available from both conditions. The houselight provided 17 lux of illumination and 27 lux when combined with the stimulus light. ANOVA revealed a significant effect of the houselight on the relative hits, Test $F(1, 21) = 5.32, p < .05$, but no effect on the relative correct rejections. ANOVA at each signal duration revealed that the effect on the relative hits was only at the 500-ms duration, Test $F(1, 21) = 11.79, p = .002$.

Group Effects During Baseline Testing

With the houselight illuminated and an ITI of 12 ± 3 s, ANOVA revealed a significant group difference in the relative hits from all signal events, Group $F(2, 18) = 3.63, p < .05$, and the relative correct rejections from all nonsignal events, Group $F(2, 18) = 4.69, p < .05$. Analyses at each signal duration showed that the group difference in relative hits was only present at the 500-ms signal, Group $F(2, 18) = 3.50, p = .05$. Pairwise comparisons showed that these group differences were only in the *Lc/+* group. In all groups, performance improved as the signal event lengthened, Duration $F(3, 54) = 103.37, p < .001$ (see Table 1).

The SB of all baseline test sessions was 0.45, which indicated a slight bias toward the right lever. This bias revealed a greater propensity for the subjects to report that a nonsignal event had

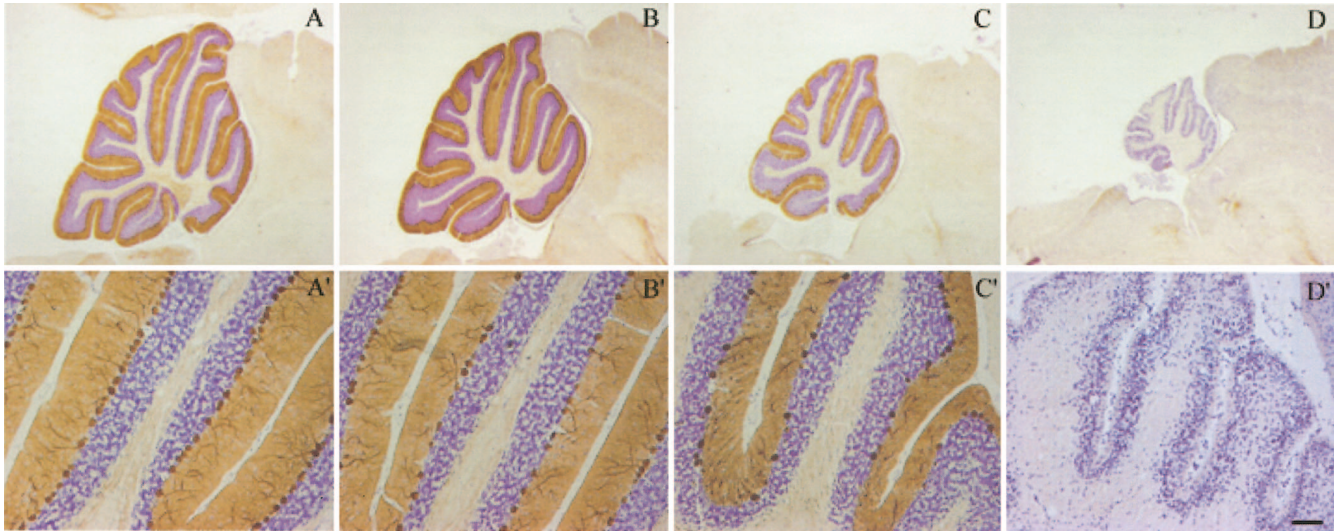


Figure 1. Photographs of cerebellar sections from *Lc/+*, *+/+*, and *Lc/+* chimeras taken at both low and high magnifications demonstrating the loss of Purkinje cells in *Lc/+* and chimeric mice compared with a control sample. Purkinje cells were stained immunocytochemically with the anti-Calbindin antibody (Chemicon) and appear dark brown in a single monolayer above the blue-stained cerebellar granule cells (cresyl violet counterstain). (A) Section from a *+/+* control cerebellum with normal Purkinje cell number and cerebellar size. (B) Section from the cerebellum of a high-percentage *+/+* chimera with a minor loss of Purkinje cells. (C) Section from the cerebellum of a low-percentage *+/+* chimera showing a major loss of Purkinje cells. (D) Section from a *Lc/+* cerebellum demonstrating the complete loss of Purkinje cells and extreme decrease in cerebellar size. Scale bar = 500 μ m A–D, 120 μ m A'–D'.

occurred and likely reflected the poor detection of signal events at the shortest durations. ANOVA revealed no differences in side bias between groups.

Several other measures were also obtained during each test session, including the number of signal and nonsignal events in which a response was not given, the total number of entries into the

food receptacle (food entries), and the latency to enter the food receptacle following reinforcement delivery (food latency). Separate ANOVAs for each of these other measures revealed a significant group difference in food latency only, Group $F(2, 18) = 3.96$, $p < .05$. Pairwise comparisons showed that *Lc/+* ($M = 4.32$ s) mice took significantly longer to reach the food magazine

Table 1
The Mean Correct Rejections and Relative Hits of Each Group in Four Sustained Attention Test Variations

Group	Correct rejections	Relative hits				
		All durations	50 ms	75 ms	100 ms	500 ms
<i>Lc/+</i>						
ITI 12 \pm 3 s	.682 (.019)	.528 (.019)	.428 (.026)	.483 (.024)	.533 (.025)	.668 (.022)
ITI 9 \pm 3 s	.688 (.018)	.577 (.019)	.501 (.025)	.545 (.024)	.607 (.023)	.717 (.022)
Visual distracter	.634 (.024)	.559 (.018)	.507 (.023)	.549 (.023)	.556 (.023)	.611 (.023)
Auditory distracter	.609 (.021)	.542 (.024)	.472 (.029)	.479 (.027)	.507 (.029)	.622 (.028)
Chimera						
ITI 12 \pm 3 s	.724 (.016)	.569 (.015)	.484 (.021)	.527 (.019)	.560 (.020)	.712 (.018)
ITI 9 \pm 3 s	.767 (.015)	.569 (.015)	.461 (.021)	.519 (.019)	.543 (.019)	.748 (.018)
Visual distracter	.709 (.019)	.547 (.015)	.467 (.019)	.494 (.019)	.537 (.018)	.689 (.019)
Auditory distracter	.753 (.017)	.482 (.020)	.421 (.024)	.444 (.022)	.458 (.024)	.604 (.023)
<i>+/+</i>						
ITI 12 \pm 3 s	.719 (.016)	.599 (.015)	.531 (.021)	.528 (.019)	.580 (.020)	.771 (.018)
ITI 9 \pm 3 s	.734 (.015)	.592 (.015)	.504 (.021)	.526 (.019)	.578 (.019)	.747 (.018)
Visual distracter	.658 (.019)	.584 (.015)	.516 (.019)	.545 (.019)	.567 (.018)	.708 (.019)
Auditory distracter	.790 (.017)	.432 (.020)	.368 (.024)	.383 (.022)	.408 (.024)	.567 (.023)

Note. There was no significant difference associated with the change in intertrial interval (ITI), but the visual distracter and the auditory distracter caused significant deficits in correct rejections and relative hits, respectively, from baseline performance without the distracters. Standard errors are shown in parentheses.

after reinforcement delivery than chimeric ($M = 1.79$ s) and +/+ ($M = 1.95$ s) mice.

The Effect of a Change in Event Rate on Test Performance

Comparisons were made between test variations in which the ITI changed from 12 ± 3 s to 9 ± 3 s. ANOVA revealed no significant differences in either relative hits or relative correct rejections between variations. Although the group differences in relative correct rejections persisted, Group $F(2, 18) = 10.77, p < .001$ (see Table 1), there was no interaction between group and condition. The change across signal durations also persisted, Duration $F(3, 54) = 177.02, p < .001$, but there was no effect of the change in event rate on signal duration.

Analysis of Trial Blocks Within Testing Sessions

To assess changes in performance within testing sessions in the baseline condition and following the change in ITI, we divided each session into three equal blocks of 48 trials. Separate ANOVAs of the results at each ITI revealed no significant changes across trial blocks in either relative hits or relative correct rejections.

The Effects of Distracters on Test Performance

The effects of visual and auditory distracters were determined by comparing performance under these conditions with baseline performance. ANOVA indicated significant differences across test variations in both the total relative hits, Test $F(2, 36) = 11.82, p < .001$, and relative correct rejections, Test $F(2, 36) = 4.08, p < .05$. However, pairwise comparisons showed that these differences were unique for each modality of distraction. When a visual distracter was used, there were significantly lower numbers of relative correct rejections ($M = 0.650$) in comparison with either baseline ($M = 0.708$) or an auditory distracter ($M = 0.724$), but when an auditory distracter was used there were significantly lower numbers of relative hits ($M = 0.458$) compared with baseline ($M = 0.574$) or a visual distracter ($M = 0.567$). These results indicate that the visual distracter caused more false alarms to nonsignal events, whereas the auditory distracter caused more misses to signal events.

ANOVA of baseline, visual, and auditory distracter conditions demonstrated significant differences between groups in relative correct rejections, Group $F(2, 18) = 5.51, p < .05$, and across signal durations, Duration $F(3, 54) = 167.97, p < .001$. With the exception of the effect of the change in durations (Test \times Duration), $F(6, 108) = 7.06, p < .001$, these differences did not interact with the change in testing condition. Table 1 demonstrates the consistency of the differences between the means of each group across testing variations. There was a significant interaction of the signal duration changes for each group in these variations (Group \times Test \times Duration), $F(12, 108) = 1.85, p < .05$.

The Effect of Visual Distracter Frequency on Test Performance

Mice were tested in a modified version of the visual distracter test variation in which each test session was divided into three

blocks with the houselight flashing at a different frequency (i.e., 0.5, 1, or 2 Hz) in each block. ANOVA demonstrated that performance was not significantly altered by the change in distracter frequency.

Comparisons of Total Purkinje Cell Number With Test Performance

Histological analysis of mice tested in the sustained attention task allowed us to make comparisons between total Purkinje cell number in all mice or just the chimeric mice and between measures of performance in each test variation using Pearson product-moment correlation coefficients. There were no significant relationships between Purkinje cell number and either relative hits or relative correct rejections from each testing condition.

Discussion

In this report, we present the results of a test of sustained attention from a mouse model of Purkinje cell loss that encompassed the full spectrum of Purkinje cells from zero to normal numbers.

Performance of Mice Versus Rats

The task that we used to assess sustained attention was very similar to a previous task described by McGaughy and Sarter (1995), which was based on the original task developed at the Environmental Protection Agency by Bushnell and colleagues (Bushnell & Kelly, 1992; Bushnell, Kelly, & Crofton, 1994). McGaughy and Sarter's study involved testing rats with three signal durations: 25 ms, 50 ms, and 500 ms. In our pilot study, mice were unable to accurately detect the signal at the 25-ms duration (data not shown). We therefore used four signal durations, with the 50-ms signal being the shortest. With this modification, 24 of 51 mice were able to successfully complete the testing procedure.

The results from testing with mice show similarities to the results from rat studies. Several rat studies have reported an improvement in performance related to (a) an increase in signal intensity or duration (Bushnell, 1999; Bushnell et al., 1994; McGaughy & Sarter, 1995, 1999; Oshiro, Krantz, & Bushnell, 2001), (b) a decrease in performance as a result of either visual or auditory distracters (McGaughy & Sarter, 1995, 1999; Oshiro et al., 2001), and (c) a decrease in performance associated with an increase in the event rate (Bushnell, 1999; McGaughy & Sarter, 1995, 1999; Oshiro et al., 2001). Our results also indicate improved performance as the signal duration lengthened and a decrease in performance associated with visual or auditory distracters. Regarding the change in event rate, we found no effect of an increase in event rate, which was possibly due to the small change and variability of our ITIs (e.g., 12 ± 3 s and 9 ± 3 s).

The Relationship Between Purkinje Cells and Sustained Attention

There were no differences between chimeric mice and +/+ controls in any of the test variations. In addition, Pearson correlations between both relative hits and relative correct rejections from each test variation and total Purkinje cell number from all

mice, or just the chimeric mice, did not reveal any significant relationships. However, Lc/+ mice, with a complete loss of Purkinje cells, did show deficits in their performance. Specifically, Lc/+ mice consistently demonstrated a greater number of false alarms in response to nonsignal events compared with controls in all testing variations.

Lc/+ mice took longer than controls to reach the food receptacle following reinforcement delivery. It was also observed that Lc/+ mice moved around more on the chamber floor because of their ataxia. Given that the loss of Purkinje cells in the nonataxic chimeric mice did not have an impact on performance, it appears that the deficits shown by Lc/+ mice were not caused by a role for Purkinje cells in sustained attention but rather by their motor impairments. It is likely that their motor impairments were also responsible for the disproportionate number of Lc/+ mice (13 of 27) that did not complete testing.

The Effect of Visual and Auditory Distracters on Sustained Attention

We assessed the effects of visual distraction using a continuously flashing houselight during task performance. Results show that this distraction caused all mice to decrease their accuracy to respond to nonsignal events, in comparison with baseline, and that changing the flashing frequency of the houselight had no further impact on performance. It is likely that the flash of the houselight was difficult for mice to dissociate from the flash of a signal event.

We assessed the effects of auditory distraction using 80 dB of white noise during signal and nonsignal events. Results show that, similar to visual distraction, auditory distraction caused decreased levels of performance in all mice, in comparison with baseline. We find it interesting that contrary to the visual distraction, these effects were caused by decreased accuracy to signal events and not nonsignal events. In addition, this decrease in accuracy was demonstrated for all signal durations.

Conclusion

In this study, we determined that mice can be successfully trained and tested in a sustained attention task, similar to that described in McGaughy and Sarter's (1995) study, but only after short signal events were modified to longer durations. It would be interesting to explore whether this finding can be generalized to all mice or whether there are variations in sustained attention that are strain specific. Regarding cerebellar function, we did not find evidence for a relationship between sustained attention and Purkinje cells.

References

- Abercrombie, M. (1946). Estimation of nuclear population from microtome sections. *Anatomical Record*, *94*, 239–247.
- Allen, G., Buxton, R. B., Wong, E. C., & Courchesne, E. (1997, March 28). Attentional activation of the cerebellum independent of motor involvement. *Science*, *275*, 1940–1943.
- Bushnell, P. J. (1998). Behavioral approaches to the assessment of attention in animals. *Psychopharmacology (Berlin)*, *138*, 231–259.
- Bushnell, P. J. (1999). Detection of visual signals by rats: Effects of signal intensity, event rate, and task type. *Behavioural Processes*, *46*, 141–150.
- Bushnell, P. J., & Kelly, K. L. (1992). Vigilance and selective attention in rats using auditory stimulus detection. *Neuroscience Abstracts*, *18*, 1062.
- Bushnell, P. J., Kelly, K. L., & Crofton, K. M. (1994). Effects of toluene inhalation on detection of auditory signals in rats. *Neurotoxicology and Teratology*, *16*, 149–160.
- Caddy, K. W., & Biscoe, T. J. (1979). Structural and quantitative studies on the normal C3H and Lurcher mutant mouse. *Philosophical Transactions of the Royal Society of London, Series B: Biological Sciences*, *287*, 167–201.
- Casey, B. J., Thomas, K. M., Welsh, T. F., Badgaiyan, R. D., Eccard, C. H., Jennings, J. R., et al. (2000). Dissociation of response conflict, attentional selection, and expectancy with functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences, USA*, *97*, 8728–8733.
- Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., et al. (1998, October 21). A common network of functional areas for attention and eye movements. *Neuron*, *21*, 761–773.
- Coull, J. T., Frackowiak, R. S., & Frith, C. D. (1998). Monitoring for target objects: Activation of right frontal and parietal cortices with increasing time on task. *Neuropsychologia*, *36*, 1325–1334.
- Goldowitz, D., Moran, H., & Wetts, R. (1992). Mouse chimeras in the study of genetic and structural determinants of behavior. In D. Goldowitz, D. Wahlsten, & R. E. Wimer (Eds.), *Techniques for the genetic analysis of brain and behavior: Focus on the mouse* (pp. 271–290). Amsterdam: Elsevier.
- Le, T. H., Pardo, J. V., & Hu, X. (1998). 4 T-fMRI study of nonspatial shifting of selective attention: Cerebellar and parietal contributions. *Journal of Neurophysiology*, *79*, 1535–1548.
- Martin, L. A., Escher, T., Goldowitz, D., & Mittleman, G. (2004). A relationship between cerebellar Purkinje cells and spatial working memory demonstrated in a lurcher/chimera mouse model system. *Genes, Brain, & Behavior*, *3*, 158–166.
- Martin, L. A., Goldowitz, D., & Mittleman, G. (2003). The cerebellum and spatial ability: Dissection of motor and cognitive components with a mouse model system. *European Journal of Neuroscience*, *18*, 2002–2010.
- McGaughy, J., & Sarter, M. (1995). Behavioral vigilance in rats: Task validation and effects of age, amphetamine, and benzodiazepine receptor ligands. *Psychopharmacology (Berlin)*, *117*, 340–357.
- McGaughy, J., & Sarter, M. (1999). Effects of ovariectomy, 192 IgG-saporin-induced cortical cholinergic deafferentation, and administration of estradiol on sustained attention performance in rats. *Behavioral Neuroscience*, *113*, 1216–1232.
- Oshiro, W. M., Krantz, Q. T., & Bushnell, P. J. (2001). Characterizing tolerance to trichloroethylene (TCE): Effects of repeated inhalation of TCE on performance of a signal detection task in rats. *Neurotoxicology and Teratology*, *23*, 617–628.
- Rees, G., Frackowiak, R., & Frith, C. (1997, February 7). Two modulatory effects of attention that mediate object categorization in human cortex. *Science*, *275*, 835–838.
- Zuo, J., De Jager, P. L., Takahashi, K. A., Jiang, W., Linden, D. J., & Heintz, N. (1997, August 21). Neurodegeneration in Lurcher mice caused by mutation in delta2 glutamate receptor gene. *Nature*, *388*, 769–773.

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