Evaluation of a behavioral method for objective vision testing and identification of achromatopsia in dogs

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Objective—To develop a quantifiable behavioral test for identification of achromatopsic dogs based on visual performance.

Animals—14 dogs.

Procedures—A 3.6-m-long obstacle-avoidance course with 6 obstacle panels was developed from a preliminary 2.4-m-long course. Achromatopsic and visually normal control dogs were run through the course at 4 ambient light intensities (from dim to bright: 0.2, 25, 65, and 646 lux). Completion of 4 runs ranging from dimmest to brightest light intensity constituted 1 complete trial. Each dog underwent 3 trials. Transit times were measured and compared between dog groups and between light intensities by use of a generalized linear model and ANOVA.

Results—At the 3 highest light intensities, the achromatopsic dogs needed significantly more time to pass through the obstacle course than the control animals. Compared with the mean transit time at the lowest light intensity, mean transit times were 2.6 times as long at 25 lux, 3.2 times as long at 65 lux, and 5.7 times as long at 646 lux. The achromatopsic dogs had signs of increasing difficulty navigating around the obstacle panels with increasing light intensities; this was not the situation for the control dogs.

Conclusions and Clinical Relevance—A 3.6-m-long obstacle-avoidance course with 6 movable obstacle panels allowed identification of achromatopsic dogs at ambient light intensities ≥ 25 lux based on transit times. This test could be helpful in the evaluation of new cone photoreceptor–specific treatments. (*Am J Vet Res* 2010;71:97–102)

The clinical, psychophysical evaluation of visual performance is generally less sophisticated in veterinary medicine than in human medicine, mostly because of limitations in the assessment of responses to visual stimuli by an untrained animal. The testing of general visual performance in dogs is usually limited to rather simple methods such as the menace response test, the visual placing reaction, and the tracking of objects such as a cotton ball or laser pointer.[1,2] In a clinical setting, dogs may be observed maneuvering around obstacles under different, often ill-defined, ambient light intensities in the examination room. Although this maze navigation test can provide useful information about the dog's visual abilities, the resulting data are generally not quantifiable.

Other ophthalmic examination techniques such as pupillary light and dazzle reflexes may help to assess parts of the visual pathways; however, these reflexes are not routed through the visual cortex and conscious visual perception is therefore not evaluated.[1,2] Electroretinography is limited to the specific assessment of retinal function.[3] In comparison, visual evoked potentials represent the voltage changes in the brain elicited by defined visual stimuli. These responses are rather small in amplitude, and their re-

Abbreviations

CNGB3	Gene encoding the β3 subunit of cyclic nucleotide-gated channel in cone photoreceptors
LCA	Leber congenital amaurosis
PVC	Polyvinyl chloride
RPE65	Gene encoding the retinal pigment epithelium-specific 65-kDa protein

Received January 9, 2009.
Accepted March 11, 2009.
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Supported by the National Institutes of Health, National Eye Institute (EY006855, EY017549, EY019304, K12 EY015398, and P30 EY001583), and the Foundation Fighting Blindness.
Presented in part at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Ft Lauderdale, Fla, April 2008.
The authors thank Drs. Gustavo Aguirre and Gregory Acland as well as Amanda Nickle, Gerri Antonini, Alice Eidsen, Tracy Greiner, Rene Santin, Michael Suplick, Jason Hinmon, and Mary Leonard for technical assistance.
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producible recording and interpretation are technically challenging, particularly in a clinical setting.[3] Modern imaging technologies such as functional magnetic resonance imaging allow detailed functional assessment of the central visual pathways.[4–6] These techniques are powerful tools, but they are associated with substantial cost and time and they require anesthetic immobilization of the animal.

Achromatopsia is characterized by the loss of cone photoreceptor function, with resulting day blindness, total color blindness, decreased visual acuity, and photophobia.[7–9] In dogs, achromatopsia is caused by either a genomic deletion (so-called null mutation, originally identified in Alaskan Malamutes) or a point mutation (so-called missense mutation, found in affected German Shorthaired Pointers) of *CNGB3*.[10] The *CNGB3* encodes the β subunit of the cone photoreceptor cyclic nucleotide-gated channel, a crucial part of the phototransduction cascade in cone photoreceptors.[11] The development of a quantifiable visual function test would add to the repertoire of analytic tools to identify dogs with achromatopsia and potentially also other visual impairments.

The purpose of the study reported here was to develop a tool for quantifiable assessment of navigational vision in dogs under different light conditions. Because our laboratories are involved in the study of disease mechanisms and treatment of achromatopsia in dogs, our goal was to obtain a practical tool to easily differentiate achromatopsic dogs from visually normal control dogs by use of visual function testing.

Materials and Methods

Animals—Fourteen purpose-bred mixed-breed dogs were used for behavioral testing. Subjects included 5 dogs (1 male and 4 females) with clinically normal vision and a mean ± SD age of 255 ± 207 days (range, 104 to 504 days) and 9 achromatopsic dogs (5 males and 4 females) with a mean age of 183 ± 171 days (range, 75 to 555 days) with the *CNGB3*-null (n = 8) or *CNGB3*-missense mutation (1). The selected dogs were purposely older than 56 to 70 days, which our experience suggests is an age range during which cone photoreceptor function becomes mostly nonrecordable in affected dogs.[8,9] For the entire duration of the study, dogs were kept indoors under the same standard light conditions that they were exposed to since birth (ie, a cycle of 12 hours of light and 12 hours of dark), with illumination during the light phase between 6 and 80 lux, depending on the location within the housing unit. This study was conducted in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and the University of Pennsylvania Institutional Animal Care and Use Committee.

To acclimate the dogs to the investigators and the testing conditions, the dogs were permitted to play in the dimly lit testing room (illumination, 0.2 lux) for 30 to 60 minutes twice weekly for 2 to 4 weeks. During this acclimation period, the dogs were conditioned to voice commands and rewards such as vocal praise, toys, and treats. Upon completion of the initial conditioning, all dogs were taken through the visual testing apparatus without any of the obstacle panels in place to make them comfortable with the surroundings.

Visual testing apparatus—An obstacle-avoidance course (2.4 m long, 1.2 m wide, and 1.2 m tall) was constructed with 6.35-mm-thick, white PVC panels. A 0.9 × 0.9-m door was cut in the front and back wall of the obstacle course to provide an entrance and exit, respectively. Three steel shelving tracks were placed at 0.6-m fixed distances across the top of the course. Polyvinyl chloride obstacle panels (0.7 m wide) were set in the course under each of the tracks with the option to slide the panels to the left or right side wall of the course, allowing a 0.5-m space through which dogs could navigate between the obstacle panel and side wall. The panel positions were changed between runs to account for learning behavior.

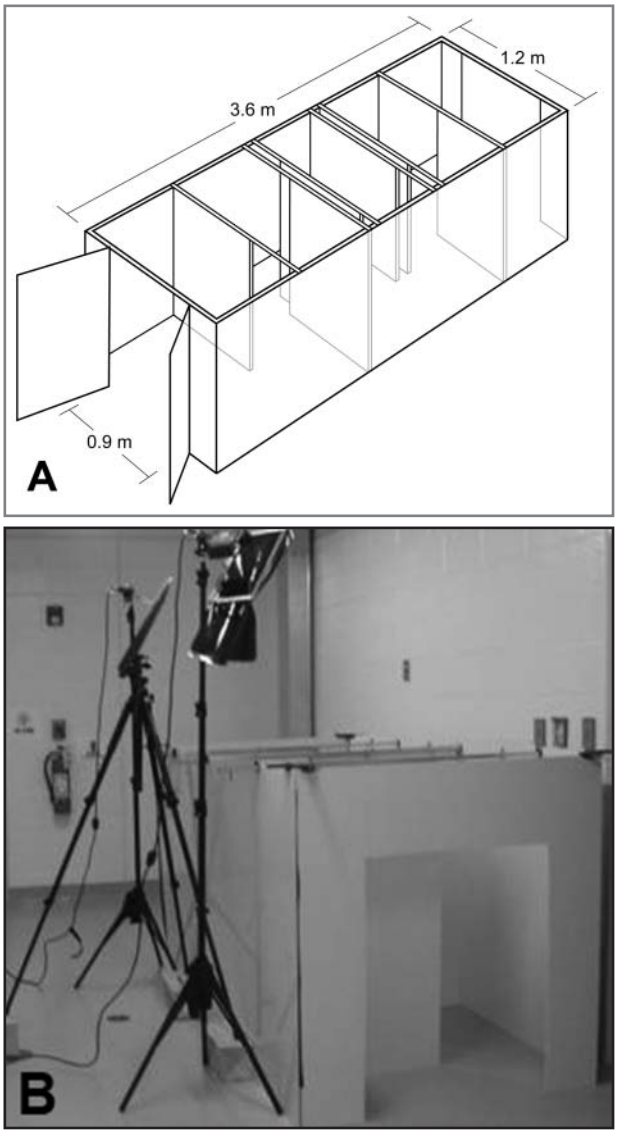

Figure 1—Diagram (A) and photograph (B) of the 3.6-m-long obstacle-avoidance course with 6 adjustable panels used to develop a quantifiable behavioral test for identification of achromatopsic dogs based on visual performance. A—The course entrance is visible, with the 2 doors on the bottom left and the exit on the top right. B—The exit opening (front) and lighting setup (left) are visible.

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After preliminary testing, the course was lengthened from 2.4 to 3.6 m by adding white PVC sheets (6.35 mm thick and 1.2 m long) to the side walls (**Figure 1**). Notches were cut along the length of the course at the upper edge of the side panels, and 6 steel tracks were placed at varying intervals (0.2, 0.4, or 0.6 m) across the top of the course. The PVC obstacle panels were again set in the course under the tracks. In addition to left and right positions, 1 of 6 panels was placed in a middle position, leaving only a 0.3-m (instead of 0.5-m) space for the dogs to pass through. Throughout the trials, the 6 obstacle panels were moved between each run by changing the side position of each obstacle (ie, to left, right, or middle) and the intervals in between the obstacles. Whenever 2 adjacent obstacle panels were only 0.2 m apart, they were never on opposite sides but rather placed either on the same side (left or right) or in the middle position, so that the dogs did not have to squeeze through the 0.2-m space between these adjacent panels. Specific obstacle panel combinations were randomly configured, and the order of these combinations was determined for each run before the beginning of the trials. This was done to prevent the dogs from memorizing the positions of the obstacle panels. All dogs were tested with the same obstacle panel combinations.

Two tungsten halogen stage lights[a] with neutral density filters were mounted on 1.8-m-tall tripods set against the side panels of the course (Figure 1). By varying the brightness of these stage lights and the overhead neon lights in the testing room, the following 4 ambient light intensities (illuminations) were defined with a photometer[b] within the obstacle course: 0.2, 25, 65, and 646 lux. Compared with outdoor ambient light conditions, the dimmest setting was similar to lighting on a clear night with a half moon and the brightest setting to lighting on a bright, overcast day. Two digital video cameras[c] were set on 1.8-m-tall tripods positioned near the entrance and the exit of the obstacle course to record all runs. The cameras contained infrared filters for filming in the dimmest light condition.

Study design—For the entire study, the operators were unaware of the genotype and disease status of the dogs. The goal was to identify the achromatopsic and visually normal dogs solely on the basis of performance in the obstacle-avoidance course. Before each trial, each dog was walked from the housing facility to the testing room in the same building and adapted for 20 minutes to the 0.2-lux illumination. Subsequently, the dog was released at the entrance of the course, and the transit time was measured off-line on film from the first forward motion to passing through the exit under each of the 4 light conditions, starting with the lowest light setting. When a dog exited the obstacle course, it received vocal praise. After completion of each run, the ambient light intensity was increased to the next degree of brightness, the obstacle panel positions were changed according to a predetermined scheme, and the dog was light adapted for 10 minutes before positioning at the course entrance for the next run. Completion of 4 runs ranging from dimmest to brightest light intensity constituted 1 complete trial. At the end of a trial, the dog received an edible treat. Each dog underwent 3 trials, with each trial on a different day, and each dog was tested with the same set of obstacle panel combinations.

An initial group of control (n = 2) and achromatopsic dogs (4) was tested in the 2.4-m-long course. Because there was no significant difference in transit time across the 4 light intensities for the achromatopsic dogs and the disease status of some dogs could not be accurately determined, the length of the obstacle-avoidance course was extended to 3.6 m and the number of obstacle panels was doubled from 3 to 6. The upgraded course was evaluated with 5 control and 5 achromatopsic dogs by use of the same study design as described for the 2.4-m-long course. Two of these control dogs had already been used for the 2.4-m-long course, and the remaining control dogs had not yet been tested.

Statistical analysis—For each dog, the mean transit time from the 3 trials at each light intensity was used for data analysis. The comparisons of mean transit times between achromatopsic and control dogs were conducted by means of a generalized linear model, which adjusted for the correlation of repeated measures at various light intensities within the same dog. Univariate and multivariate (adjusted by age and sex) analyses were performed. A 1-way repeated-measures ANOVA was performed for each dog group separately to determine whether the transit time varied across the 4 light intensities and whether there was a linear trend from the lowest to the highest illumination. For each of the dog groups, the mean transit times were compared between lowest and highest light intensities with a paired *t* test. Mean ages and sex distributions were compared between the achromatopsic and control groups with the 2-group *t* test and Fisher exact test, respectively. A 2-sided P value ≤ 0.05 was considered significant for all comparisons. Results are reported as mean ± SEM.

Results

Preliminary testing in 2.4-m-long obstacle-avoidance course—The 2.4-m-long course was used to test 4 achromatopsic and 2 control dogs whose ages ranged from 131 to 555 days. There was no significant difference in mean age ($P = 0.51$) or sex distribution ($P = 0.47$) between these groups. The respective mean ± SEM transit times for control versus achromatopsic dogs at each light intensity were as follows: 0.2 lux, 4.00 ± 1.00 seconds versus 4.44 ± 0.29 seconds ($P = 0.55$); 25 lux, 3.75 ± 1.11 seconds versus 8.75 ± 3.55 seconds ($P = 0.08$); 65 lux, 3.13 ± 0.13 seconds versus 12.50 ± 4.00 seconds ($P = 0.001$); and 646 lux, 3.38 ± 0.90 seconds versus 14.30 ± 5.77 seconds ($P = 0.01$; **Figure 2**). The mean transit time for achromatopsic dogs was 4.0 times as long as that for control dogs at 65 lux and 4.2 times as long at 646 lux.

In addition to the effect of increasing light intensity on transit time in achromatopsic dogs, at higher light intensities, it was obvious that these dogs had difficulty navigating the course. However, we could not identify additional quantifiable response variables. For example, the number of collisions with obstacle panels was not a useful response variable to identify achromatopsic dogs because some of these dogs were cautious and, despite visual impairment, rarely bumped into the

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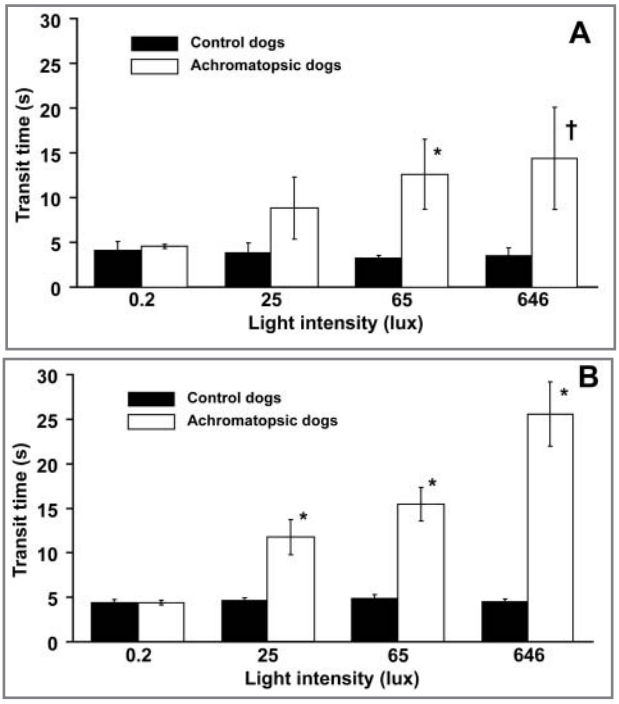

Figure 2—Mean ± SEM transit times for achromatopsic and control dogs as a function of light intensity in a 2.4-m-long (A; 2 control and 4 achromatopsic dogs) and 3.6-m-long (B; 5 control and 5 achromatopsic dogs) obstacle-avoidance course. *†Values are significantly (*$P < 0.001$; †$P < 0.01$) different between groups at the indicated light intensity.

Figure 3—Representative images extracted from video recordings of an achromatopsic dog exhibiting behavior typical of achromatopsic dogs in an obstacle-avoidance course at high (646-lux) light intensity. A—Dog is bumping and touching the obstacle panel. B—Dog is leaping with forefeet ahead to identify the passage around the obstacle panel.

obstacles. Despite the significant difference in transit times between control and achromatopsic dogs at the 2 higher light intensities, high variability in transit times of achromatopsic dogs occasionally prevented the determination of disease status. Surprisingly, there was no significant difference in transit times across the 4 light intensities for the control dogs ($P = 0.86$) and the achromatopsic dogs ($P = 0.21$). Even though the power to detect a significant difference in results could have improved for the achromatopsic dogs by increasing the sample size, we decided to raise the degree of course difficulty by making the course longer and adding additional obstacles.

Testing in 3.6-m-long obstacle-avoidance course— A larger group of achromatopsic (n = 5) and control (5) dogs between 75 to 504 days of age was tested with the 3.6-m-long course. There was no significant difference in mean age ($P = 0.15$) and sex distribution ($P = 0.52$) between the 2 groups. Mean transit times for control versus achromatopsic dogs in this expanded course were as follows: 0.2 lux, 4.37 ± 0.29 seconds versus 4.26 ± 0.26 seconds ($P = 0.78$); 25 lux, 4.58 ± 0.32 seconds versus 11.70 ± 1.96 seconds ($P < 0.001$); 65 lux, 4.81 ± 0.41 seconds versus 15.40 ± 1.91 seconds ($P < 0.001$); and 646 lux, 4.45 ± 0.27 seconds versus 25.50 ± 3.64 seconds ($P < 0.001$). The mean transit time for achromatopsic dogs was 2.6 times as high as that for control dogs at 25 lux, 3.2 times as high at 65 lux, and 5.7 times as high at 646 lux. When analyzing transit times within dog groups, we found a significant ($P = 0.04$) increasing linear trend in mean transit times from lowest to highest light intensity and a significant ($P = 0.04$) difference in mean transit times between the lowest and highest light intensities in the achromatopsic dogs, but neither of these effects was evident in the control dogs ($P = 0.54$ and $P = 0.80$, respectively). The increasing transit times for achromatopsic dogs suggested that rod photoreceptor–mediated vision was saturated at light intensities ≥ 25 lux.

Similar to their behavior in the 2.4-m-long course, the achromatopsic dogs appeared to have increasing difficulty navigating around the obstacle panels at the higher light intensities.[12] Again, we could not identify additional quantifiable response variables (eg, number of collisions with the PVC panels) that would have allowed identification of dogs with achromatopsia. Several achromatopsic dogs moved cautiously within the course and did not bump into obstacles despite severe visual impairment. Interestingly, the achromatopsic dogs appeared to use alternative strategies for navigation at brighter light intensities.[12] For example, the dogs put their noses to the ground as though they were using olfactory cues for navigation[12] or often jumped as if trying to feel the panels with their forefeet (**Figure 3**).

Discussion

Achromatopsia, also called rod monochromacy, is a rare autosomal recessive disease in humans characterized by cone photoreceptor nonfunction and associated

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loss of day vision, complete color blindness, reduced visual acuity, and photophobia.[7,13,14] The disease has also been identified in various dog breeds such as Alaskan Malamutes[8–10,15] and German Shorthaired Pointers.[10] In most of those dogs, the classic disease phenotype of day blindness develops between 8 and 12 weeks of age, soon after retinal differentiation is complete,[8,9] but affected dogs do not lose eyesight because of retained rod photoreceptor function, and they remain ophthalmoscopically normal throughout life.[8] Although achromatopsic dogs can be easily identified by loss of cone-mediated electroretinographic responses[9,16] or qualitative recognition of day blindness by simple maze navigation testing,[17,18] our future endeavor to develop and evaluate new treatments for this disease will require a quantifiable visual function test. The goal of the present study was to develop a behavioral test for the objective, quantifiable assessment of navigational vision, which could be used for the recognition of day-blind dogs.

In the preliminary phase of the study, we used a 2.4-m-long obstacle-avoidance course with 3 obstacle panels at fixed distances. Each obstacle panel could be set to either the left or right position. The mean transit time of achromatopsic dogs was significantly longer (approx 4 times as long) than that of visually normal control dogs at the 2 brightest ambient light intensities (65 and 646 lux). However, there was no significant difference in transit times between light intensities for the achromatopsic dogs. In addition, the large variability in transit times of the achromatopsic dogs made it difficult to clearly identify some of the day-blind dogs. Therefore, the course was modified by making it 1.2 m longer, doubling the number of obstacle panels to 6, varying the intervals between the obstacles panels, and adding the option of a third, middle position for 1 of the 6 panels.

In the upgraded 3.6-m-long obstacle-avoidance course, the achromatopsic dogs had significantly longer transit times than control dogs at the 3 brightest ambient light conditions. In contrast to findings with the shorter obstacle-avoidance course, there was a significantly increasing linear trend in transit times from the lowest to the highest light intensity for achromatopsic dogs but not control dogs. Therefore, the 3.6-m-long obstacle-avoidance course fulfilled our requirements to clearly identify achromatopsic dogs, particularly at 646 lux, which corresponds to the brightness outside during a bright overcast day. Our results suggested that rod photoreceptor–mediated vision is saturated in dogs at ambient light intensities ≥ 25 lux, adding to other data regarding behavioral day blindness in achromatopsic dogs.[17,18]

Although other investigators have used the number of collisions with obstacles as a measure of visual performance in dogs,[19–21] we were unable to use that measurement as a quantifiable response variable. Even though the day-blind dogs clearly had difficulty finding their way around the obstacle panels under bright ambient light, several of these dogs maneuvered cautiously enough to avoid bumping into any of the PVC panels. Video recordings of the dogs' performance are available elsewhere.[12] Some of the nonquantifiable signs of visual impairment included pacing back and forth in front of an obstacle, lowering of the head in search of olfactory cues, and leaping with both forefeet ahead in an attempt to feel the obstacle panel (Figure 3).[12]

One of our concerns before beginning the experiments was that the dogs would find their way around the obstacles via their excellent sense of smell. While passing through the vision testing apparatus, each dog most likely left some olfactory cues within the obstacle-avoidance course. Our results of longer transit times of achromatopsic dogs with increasing brightness suggested that these olfactory cues were useless to help dogs navigate through the course, probably because of the constant change in obstacle panel combination.

Behavioral testing has been conducted before to evaluate certain aspects of canine vision such as color perception,[22] visual acuity,[23] and brightness discrimination.[24] Training dogs for such specific tests is labor-intensive and time-consuming. Although it would be desirable to assess more specific components of cone photoreceptor–mediated vision in achromatopsic dogs, such as color discrimination and visual acuity, our goal was to develop a test that was easy to perform without requiring lengthy, labor-intensive training of the dogs. Once the dogs were acclimated to the testing environment (ie, investigators and surroundings), they were able to perform the test without any previous training. Achromatopsic humans report that colored objects appear in shades of gray.[7] Therefore, rather than using colored obstacle panels, the entire obstacle-avoidance course was built with color-neutral, uniform white PVC panels.

With the emergence of new gene therapies for treatment of inherited retinal diseases, the demand for behavioral vision tests has increased to complement other important functional testing procedures such as electroretinography and pupillometry. The following behavioral vision tests have recently been used to evaluate successful outcome of retinal gene therapy in animals: optomotor responses to a rotating sine-wave grating in mice with achromatopsia[25] and maze navigation in dogs with LCA caused by a mutation in *RPE65* (*RPE65*-LCA).[19–21] In most reported maze tests for dogs, the specific setup of the course and the obstacles is not precisely defined, and the assessment of the dogs' visual performance is mostly subjective. We used one of the maze navigation setups[19] as a template from which we developed and expanded our obstacle-avoidance course. In retinal gene therapy trials in human patients with *RPE65*-LCA, psychophysical evaluations of visual performance and treatment outcome have included visual acuity[26–28] and testing of visual field,[26,27] measurement of contrast sensitivity,[27] and testing of navigation through an obstacle course[28] or simulated street scene.[27]

An elegant vision testing apparatus has been described for objective assessment of navigational vision in dogs.[29] The device consists of a junction box with 4 exit tunnels. The dogs are placed in the junction box and given 1 vision-based choice for exit. A dog's first choice of tunnels and time to exit are recorded. This testing apparatus has been evaluated in dogs with 2 types of retinal disease: rod-cone dystrophy 3 caused by a null mutation in the gene encoding the α subunit

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of rod cyclic GMP-specific phosphodiesterase (*PDE6A*), originally identified in Cardigan Welsh Corgis,[30] and *RPE65*-LCA, originally identified in Briards.[31,32] In contrast to our achromatopsic dogs, the rod-cone dystrophy 3–affected and *RPE65*-LCA–affected dogs are more severely visually impaired in dim light than they are in bright light.[29] Future studies may reveal whether ambient light intensity in the tunnel is sufficiently bright to identify achromatopsic dogs in a 4-choice vision-assessment system. Similarly, our obstacle-avoidance course needs to be evaluated for testing of dogs with primary rod photoreceptor diseases to determine whether use of the course can also reliably detect impairment of scotopic vision.

a. Tota-light, Lowel Light Inc, Brooklyn, NY.
b. ILT1700 Research Radiometer/Photometer, International Light Technologies Inc, Peabody, Mass.
c. Sony Handycam DCR-DVD108 with Nightshot mode, Sony Corp, Tokyo, Japan.

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