Cortical Recovery Following Gene Therapy in a Canine Model of Achromatopsia

Abstract: 56.348

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Purpose

To measure the cortical response to visual stimulation in dogs with hereditary loss of retinal cone function using rod- and cone-directed stimuli.

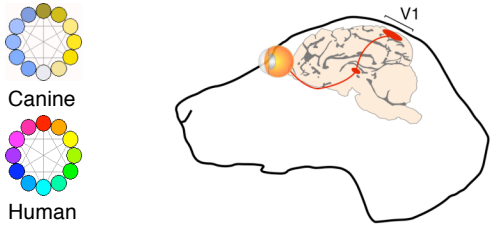

Figure 1. Canine and human color perception (left), and localization of the canine primary visual cortex (V1, right).

Methods

Subjects: Two normal dogs (*CNGB3*-null mutant carriers), 5 achromatopsia-affected dogs (*CNGB3* mutants with S- and L/M-cone dysfunctions), and 2 *CNGB3* mutants treated at 1.5 and 3 months of age (recovered L/M-cone function demonstrated by ERG) were studied using fMRI.

Gene therapy: Prior to imaging, the treated animals received unilateral recombinant adeno-associated virus (rAAV) subretinal injections containing human *CNGB3* cDNA. An L/M specific promoter was used.

Methodology: Rod- and L/M cone-directed stimuli were developed using the silent substitution method, determined with respect to published spectral sensitivity properties of the canine L/M-cone, S-cone, and rod opsins.

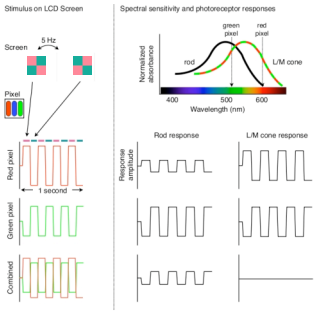

Figure 2. Silent substitution illustrated for two primaries. The experiment modulated three primaries to produce (e.g.) rod-directed responses and attenuated L/M and S-cone responses.

Visual stimuli: Visual stimulation was a 4-quadrant checkerboard, 5 Hz flicker presented for 30 seconds, alternating with a gray screen. Scanning was conducted with low (0.41 cd/m^2) and high (1194 cd/m^2) average luminance stimuli. These levels correspond to scotopic (rod) and photopic (cone) vision, respectively.

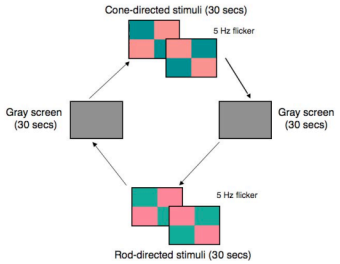

Figure 3. The stimulus presentation.

fMRI scans: Cortical responses were gathered using a 3 Tesla scanner, 3 mm isotropic voxels, at TR of 3 seconds for a total of 60 minutes of scanning per animal. The animals were sedated with Ketamine and Valium, supported with positive pressure ventilation with 100% O_2

Results

Following transformation of functional data to a canine digital atlas, functional activation was observed bilaterally within the primary visual cortex. Supra-threshold response volume was measured within a pre-defined V1/V2 ROI.

Example of an achromatopsia-affected canine:

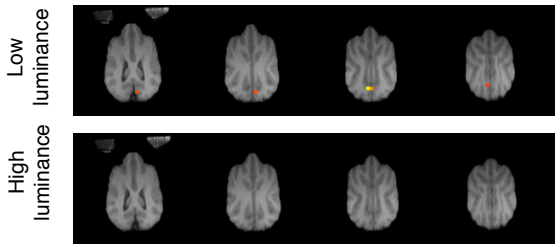

Figure 4. Cortical responses were greater for low luminance (top) than high luminance (bottom), combining across rod- and cone-directed stimuli.

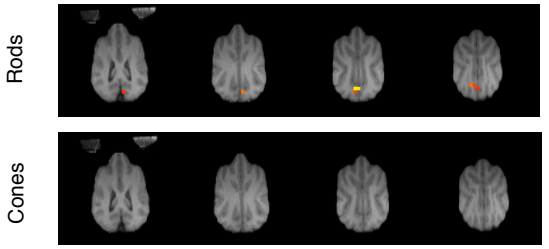

Figure 5. Within the low luminance condition, cortical responses were present for the rod-directed stimulus (top), but attenuated for the cone-directed stimulus (bottom).

Population level: The spatial extent of the supra-threshold response to high luminance, cone-directed stimuli in the normal and the treated animals was double that of the affected *CNGB3* mutants (310 mm^3 *vs.* 140 mm^3, p=0.068). No differences were observed for the rod-directed stimuli or at low luminance.

Conclusions

Rod- and cone-directed cortical responses can be identified and studied in a canine model of achromatopsia.

In *CNGB3* mutant canines, cortical responses to a cone-directed stimulus are attenuated.

Future studies will examine affected animals pre- and post-treatment to directly test for restoration of L/M-cone cortical responses.

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