Investigating color vision using fMRI: Rodent vs Primate

A. P. Salzwedel[1], M. Mauck[2], J. Kuchenbecker[3], C. Pawela[1], J. Hyde[1], M. Neitz[3], and J. Neitz[3]
[1]Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States, [2]Department of Ophthalmology, Cell Biology, Neurobiology, and Anatomy, Medical College of Wisconsin, Milwaukee, WI, United States, [3]Ophthalmology, University of Washington, Seattle, WA, United States

Introduction—Animal models are often sought after in neuroimaging studies for their high throughput capabilities and relative ease of physical, genetic, and pharmacological manipulation. Unfortunately, investigators can be faced with the tough decision of which animal model to implement, specifically regarding non-primate small mammals (rats, mice, etc) versus non-human primates. This decision is made difficult for a plethora of reasons, ranging from cost and protocol differences to potentially fundamental biological variations. Ideally, if the neural system of interest is similar enough between two species, the cheaper and more convenient of the two should be actualized. Ease of implementation aside, evaluating multiple species lends itself towards more profound thoughts, specifically those involving evolutionary considerations. In this abstract we present a comparative study of the visual systems between rats (Rattus norvegicus) and squirrel monkeys (Saimiri sciureus) using ultrahigh resolution (9.4T) functional magnetic resonance imaging (fMRI) and pharmacological intervention. More specifically, the neural pathway underlying wavelength discrimination (i.e. color vision) was investigated using the well studied metabotropic glutamate receptor agonist AP4. Here we present plausible evidence for homogeneity between these two species in this area of research.

Theory—It has long been appreciated that the ability to discriminate light based on wavelength (color) arises from the neural comparison of spectrally distinct photoreceptors (cones). Most mammals are dichromatic in nature, possessing the neural machinery capable of comparing the responses from two spectrally distinct cone types, short (S-) versus long (L-) wavelength sensitive, resulting in a system that can discriminate 'blue-yellow'—Fig. 1 *Left*. Spectrally opponent-ganglion cells are believed to be the logical candidates for providing the initial neural substrate for this color vision. In primates, the most prominent ganglion cell-type that responds in an opponent manner to short vs. long-wavelength light is the small bistratified ganglion cell (SBC)—Branch 1, Fig. 1 *Right*. This pathway, S-cone to S-cone-bipolar-cell to small-bistratified-ganglion-cell is the only characterized S-cone selective circuit known to exhibit such spectral opponency, presumably forming the cellular basis for 'blue-yellow' color vision. One can challenge this hypothesis given the unique wiring of the circuit, specifically at the S-cone-bipolar cell junction. This synapse is mediated by a metabotropic glutamate receptor (mGluR6), which can be blocked vitreously with AP4, effectively removing S-cone input to the SBC. If this circuit is responsible for the sensation of 'blueness', then S-cone isolating stimuli under blockade should produce little activity in the visual cortices. Furthermore, despite demonstration of the SBC in primates, its existence in non-primate mammals has been questioned, thus bringing about an evolutionary debate. Probing this circuit in these models, in theory, should shed light on important questions regarding color vision in addition to addressing the plausibility of using rodents over primates in this area of research.

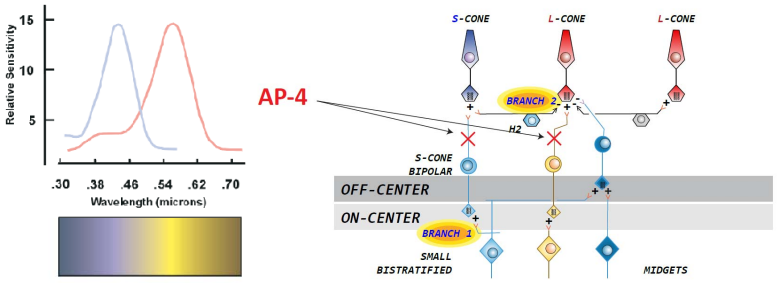

Figure 1: *Left*—Spectral Sensitivities of S- and L-cones and corresponding equal energy spectrum. *Right*—S-cone circuitry.

Methods—Both rodent and primate were injected with AP4 in the right eye. Under full field illumination of both eyes, brain responses from the treated eye were primarily sent to the left side of the brain (*note:* special contact lenses were needed in the primate to block light from the temporal hemifield). All experiments were performed in a Bruker 9.4 T small-animal scanner. For the fMRI experiments, a boxcar paradigm was used; three on/off cycles (20 s on/40 s off), where on-periods elicited S-cone isolation via silent substitution. Imaging parameters: *Rodent*—RARE: 256 x 256, TE = 50.8 ms, # Slices / ST = 15 / 1 mm, FOV = 35 mm. EPI: 96 x 96 zero filled to 128 x 128, TR = 2 s, TE = 18.8 ms, *Primate*—RARE: 256 x 256, TE = 50.8 ms, # Slices / ST = 20 / 1 mm interleaved (40 mm coverage), FOV = 60 mm. EPI: 64 x 64, TR = 2 s, TE = 18.8 ms. EPI trials were averaged for each animal and registered to the RARE anatomy. Cross-correlation analysis was carried out in AFNI with the block design modeled as a hemodynamic response function serving as the regressor.

Results—Neocortically (in red), each species exhibits equal, if not greater, BOLD activation under S-cone isolating stimuli: AP4 (left side) vs Control (right side).

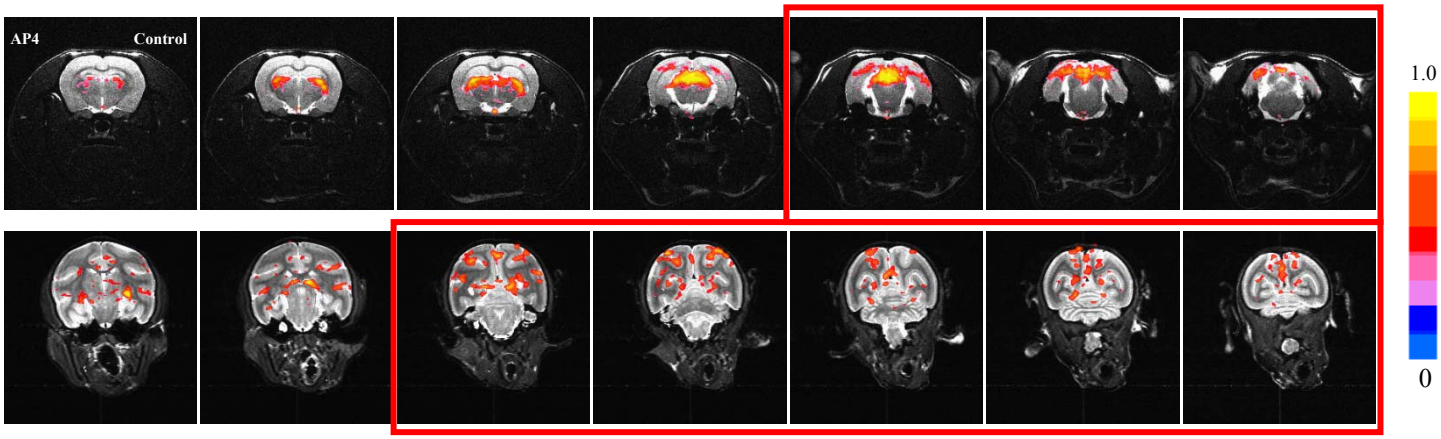

Figure 2: Activation map of BOLD response (p = 0.005) to S-cone isolating stimuli under AP4. Rodent (*Top*) vs Primate (*Bottom*). Sample Information: Rodent n = 2, # of Trials = 29, Primate n =1, # of Trials = 6.

Discussion—These results provide evidence against the SBC's role in the excitatory ('blue') aspects of S-cone vision. In actuality, "knockout" of the SBC produces excitation at the level of the cortex, indicating a potential inhibitory role. The alternative theory is that the sensation of blueness is mediated by a different pathway. Based on known circuitry, the best candidate for generating this response is horizontal cell feedback from S-cones onto neighboring L-cones—Branch 2, Fig. 1 *Right*. If true, an alternative role for the small bistratified ganglion cell is needed. Whatever the case maybe, one thing seems for certain; this mechanism appears to be conserved across these species, supporting the idea of using rodents over primates in our economically challenged lives.