Neuroscience 296 (2015) 110–115

WHAT STUDIES OF MACAQUE MONKEYS HAVE TOLD US ABOUT HUMAN COLOR VISION

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Abstract—Animal models are a necessary component of systems neuroscience research. Determining which animal model to use for a given study involves a complicated calculus. Some experimental manipulations are easily made in some animal models but impossible in others. Some animal models are similar to humans with respect to particular scientific questions, and others are less so. In this review, I discuss work done in my laboratory to investigate the neural mechanisms of color vision in the rhesus macaque. The emphasis is on the strengths of the macaque model, but shortcomings are also discussed.

This article is part of a Special Issue entitled: Contributions From Different Model Organisms to Brain Research.

Key words: color, vision, monkey.

INTRODUCTION

A broad goal of neuroscience is to understand how the brain operates in states of health and disease. This goal is sufficiently lofty, and the brain sufficiently complex, that no single line of research can achieve it alone. Instead, scientific progress is made through inquiry into a variety of specific questions, using a variety of techniques and, frequently, animal models. In this review, I discuss research into the color vision system of macaques, focusing on recent work from my own lab as one example of how this model can be used to reveal how neural signals guide behavior.

Mammalian vision begins with the absorption of light by photosensitive cells at the back of the eye. In most mammals, daytime vision is mediated by two types of cone photoreceptor: one sensitive to short wavelengths, the other sensitive to longer wavelengths. The fact that the cone types are maximally sensitive to different wavelengths gives mammals an important ability: to dissociate light intensity from spectral content. When a light varies in intensity – say, when a cloud passes in front of the sun – activity in all cones changes (approximately) proportionally. This change is relayed to the brain and is interpreted as a change in luminance. If the spectral content of a light changes – say, as the setting sun's rays are filtered progressively by the atmosphere – activity can change across cone types *dis*proportionally. Disproportionate changes in cone activities often lead to colored percepts. Color vision is thus a perceptual experience associated with a comparison of signals across different classes of receptor. Similar comparisons are likely to occur elsewhere in the nervous system, and understanding how such comparisons mediate color vision may guide our understanding of neural signal processing more generally.

Humans have three distinct types of cone photoreceptor (as do other catarrhine primates; for a scholarly review of the evolution of primate cones, the interested reader is referred to Jacobs, 2009). These three cone types are named after the wavelengths to which they are maximally sensitive: the L-, M-, and S-cones are maximally sensitive to long, medium, and short wavelengths, respectively. By comparing signals across all three cone types, the trichromatic visual system supports a rich gamut of color experiences. Some non-primate species may enjoy an even richer color experience: most birds and reptiles have four or five cone types, and the mantis shrimp has 12.

The similarity between the human and macaque visual systems goes beyond trichromacy. The absorption spectra of the three types of cone in macaques and humans are very similar (Bowmaker, 1990). Macaque and human visual systems are anatomically similar at the level of the retina (Dacey, 2000), lateral geniculate nucleus (LGN) (Garey et al., 1991), striate cortex (V1) (Casagrande and Kaas, 1994; Bernard et al., 2012), and early extrastriate cortex (Orban et al., 2004). Area V1 of macaques and humans stains similarly (but not identically) for cytochrome oxidase (Horton and Hubel, 1981; Horton and Hedley-Whyte, 1984; Preuss et al., 1999), an enzyme whose expression correlates with activity level and, for reasons that are not understood, domains that appear particularly relevant to color processing (Livingstone and Hubel, 1984; Ts'o and Gilbert, 1988). Chromatic detection and discrimination thresholds are similar in humans and macaques

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Abbreviations: LGN, lateral geniculate nucleus; V1, striate cortex.

http://dx.doi.org/10.1016/j.neuroscience.2014.10.007
0306-4522/

(De Valois et al., 1974; Merigan, 1989; Kalloniatis and Harwerth, 1991; Gagin et al., 2014). Damage to homologous areas of the macaque and human temporal lobe result in similar visual deficits, including deficits in color processing (Heywood et al., 1995). Collectively, this body of work demonstrates the utility of the macaque model for studying color vision and supports the idea that what we learn about color processing in the macaque will transfer directly, or nearly so, to the human.

Over the past several decades, a standard model of the first stages of color processing has emerged (De Valois and De Valois, 1993; Lee, 1996). According to this model, signals from the L- and M-cones are combined roughly additively and transmitted through the magnocellular layers of the LGN. This rapidly conducting pathway plays an important role in the perception of luminance, especially luminance-defined patterns in motion. In parallel with the magnocellular pathway, the parvocellular pathway combines L- and M-cone signals antagonistically to convey chromatic information and fine-scale luminance information to the LGN. Finally, at least two more anatomically distinct channels carry signals from the S-cones. These S-cone-dominated channels also receive inputs from a combination of L- and M-cones with opposite sign, although exactly what contribution each cone type makes to this combination is still being worked out (Tailby et al., 2008a; Martin and Lee, 2014; Miyagishima et al., 2014).

Why S-cone signals are processed differently from L- and M-cone signals is presumably related to the fact that L- and M-cones diverged from a common ancestral cone type relatively recently. Prior to this divergence, all mammals were probably dichromats, with a set of S-cones and another set of cones that was sensitive to longer wavelengths. By comparing signals between these two cone types, these animals would have been able to distinguish lights based on the proportion of long and short wavelengths. The addition of a third cone type allowed for a finer spectral analysis; it is in part due to this finer spectral analysis that nearby wavelengths in the yellow part of the spectrum are readily distinguishable to us. Color vision, as we experience it, is thus the product of a relatively new pathway, which pits L- and M-cone signals against each other, laid down on top of an evolutionary older pathway, which compares S-cone signals to a combination of L- and M-cone signals. By studying how signals from the old and new pathways interact, we have an exciting opportunity in color vision to learn how evolution shapes neural signal processing and the perception that results from it.

Cone signal combination is relatively well understood in the retina and LGN, but is less well understood at the next stage of visual processing, in area V1. This is the frontier that my lab has been working on. One approach we have taken is to probe V1 neurons with low contrast stimuli. We reasoned that color processing in V1, though quite complicated at high contrasts, may be simpler at low ones (many nonlinear systems behave approximately linearly in response to small perturbations). For example, human color vision behaves nonlinearly at high contrasts, but psychophysical chromatic detection thresholds can be described with a simple, linear mathematical model. According to this model, chromatic detection occurs whenever the difference between L- and M-cone signals reaches a threshold or whenever a difference between S-cone signals and a sum of L- and M-cone signals reach a threshold. The crossing of these two different thresholds is associated with different chromatic percepts in humans (Mullen and Kulikowski, 1990). These, and related observations, have led to the idea that signals carried by the new and old color pathways are detected by entirely separate populations of neurons. Our data, however, are inconsistent with this hypothesis (Hass and Horwitz, 2013).

We tested this hypothesis with an experiment that exploited two advantages of the macaque model in addition to those previously mentioned. First, macaques can be trained to perform chromatic detection tasks, and in such tasks the old and new color pathways appear to contribute to performance similarly to the way they do in humans (Krauskopf et al., 1982; Stoughton et al., 2012). Second, using extracellular electrodes inserted directly into the brain, we can record the electrical activity of individual neurons during task performance, giving us the opportunity to correlate neuronal events with behavioral ones.

We recorded from V1 neurons as a rhesus macaque reported the location of a faint chromatic flash. To our surprise, some individual V1 neurons responded to threshold-contrast signals whether carried by the new or the old pathway, in other words, whether the contrast was between the L- and M-cones, or between the S-cones and the other two (Fig. 1). This result shows that even at low contrasts, the new and old pathways converge onto individual V1 neurons.

We followed up this result by recording the responses of V1 neurons to stimuli that were identical to the ones we had used in the psychophysical experiments, but varied over a wider range of color and contrast. In these experiments, we presented visual stimuli and recorded neuronal responses but did not require the macaques to make psychophysical judgments. The only behavior required was visual fixation on a small dot, a behavior that a trained macaque can perform, with brief breaks, for hours.

Consistent with the neuronal sensitivity we had observed previously, we found a population of V1 neurons that were very broadly tuned for color. When represented in a 3D cone contrast space, the collection of stimuli that excited these neurons (at an arbitrary level set by the experimenter) traced out an ellipsoid (Fig. 2A). This suggested that some V1 neurons compute the functional equivalent of a sum of squared LGN signals (Horwitz and Hass, 2012). This quantity contains much information about the contrast of a stimulus, but relatively little about its color. Accordingly, neurons of this type could support performance on a chromatic detection task, but are unlikely to contribute significantly to hue perception. Color vision is not a monolithic entity, but rather a collection of distinct but related abilities, some of which (e.g. detection) are easier to study in the macaque than others (e.g. color naming).

Other V1 neurons that we investigated appeared to compute a sum of cone signals without the squaring, in