National Eye Institute

2019 Marmoset Community White Paper

The core mission of the National Eye Institute (NEI) is to support research on the mechanisms underlying visual perception, from the early stages of processing in the eye to downstream processes in the lateral geniculate nucleus, primary visual and extrastriate cortex, and including areas involved in higher order visual processes such as visual attention and the control of eye movements. Natural selection has endowed primates, including humans, with specializations that affect visual processing in all these areas such as, critically, the fovea, which has an outsized impact on the way visual information is processed, not simply because it yields higher acuity than any other mammal, leading to fine spatial form (shape) processing (104), but because it fundamentally changes how primates use their eyes to acquire information about the world. The primate brain has a network of oculomotor areas (105) and efficient strategies for moving the eyes so that the fovea is rapidly positioned over targets of interest. Rapid eye movements (saccades), are made two to three times every second as the brain samples the visual scene, and these signals are smoothly integrated across time so that it looks to the observer as though a wide visual field is seen crisply during a period of viewing. The areas governing the planning of saccades also play a critical role in the deployment of visuospatial attention, which strongly influences visual processing (106). Eye movements are also critical for visuo-motor manipulations during tool use and face recognition during social interactions. Relative to other mammals, primate vision is defined by these specializations along the full extent of the visual pathway from enhanced low-level retinal processing through high-level visual abilities. Thus vision research in non-human primates affords clear advantages over rodents. Both Old- and New-world monkeys have critical roles to play in the study of primate vision, but marmosets have several practical advantages: they are economical to house and easy to handle, and lack B-virus. Further, as detailed below, the marmoset has additional advantages over other primate models for vision research in multiple areas:

<u>Development</u> **-** Their short developmental timescale (reaching sexual maturity ~3x faster than macaques) allows study of postnatal development in the early visual system, and they offer interesting opportunities for developmental studies of color vision, as they exhibit genetic polymorphisms that affect the long-wavelength sensitive cones, yielding both dichromats (all males, some females) and some trichromats (some females) (107).

<u>Mapping</u> - The lissencephalic brain of the marmoset places multiple areas (such as V2, MT, face patches in IT, FEF) on the surface of the brain, where they are readily accessible for laminar recordings, array recordings, intrinsic imaging, fluorescent calcium imaging, and surface-based optogenetics (10, 12-14, 54, 108). The smaller brain of the marmoset makes large-scale mapping more efficient. Studies in Japan have already shown the promise of large-scale mapping techniques such as diffusion tensor imaging and widefield imaging.

<u>Behavior</u> – Like macaques, marmosets readily accept head restraint, a prerequisite for some approaches to electrophysiology and imaging (24) and can readily perform tasks requiring sensory discrimination (43). Marmosets make saccadic and smooth pursuit eye movements (41, 42) and preserve the use of eye movements to

explore visual scenes and the relationship between saccadic velocity and displacement (43-45). Marmosets naturally exhibit a rich visuo-social behavior that in many respects parallels human.

Disease – Treatments for debilitating diseases like blindness and retinal degeneration benefit from studying animals whose retinae are similar to those of humans. Marmosets, macaques, and humans have very similar foveal cone densities though marmosets have higher cone density in the visual periphery (109). The rapid reproductive cycle of the marmoset and lower cost of housing relative to the macaque is an advantage when testing novel treatments such as gene therapy and neuroprosthetics where costs may be prohibitive in a macaque.

Breadth of Current Research. The breadth of research related to the mission of NEI Eye currently underway in marmosets is notable, ranging from disease modeling of the visual periphery to higher level visual processing. For example, myopia (nearsightedness) is a prevalent disease of the eye that affects >20% of the human and can develop throughout life. Work has been done in marmosets studying how corrective optics early in development can affect the evolution of nearsightedness (Troilo & Judge, *Vision Research* 1993). Ongoing work in marmoset is studying the genetic markers and the molecular signaling pathways involved in myopia so that potential therapeutic targets can be identified (110). Recent work in marmosets has also begun to show how interactions between cortical areas affect visual processing elucidating the long debated role of cortical feedback in vision. Using novel optogenetic techniques for circuit dissection, the specific effects of long-range projections from V2 on V1 function were demonstrated advancing on work using more classical techniques in macaques (14). Moreover, visual face processing is important in primate social interactions and developmental prosopagnosia and autism are examples of specific disorders of face recognition afflicting a large fraction of the human population. Marmosets are highly social (4) and, like humans, are highly attentive to faces (43, 45) because they convey meaningful social information (111) and exhibit specialized regions for face processing in high-level visual cortex (53). Studies of this face-patch network are poised to expand with ongoing efforts to developed transgenic marmoset models of autism disorder.

The Future. As a rapidly emerging model system, marmosets are likely to play a critical role in elucidating the intricacies of the primate visual system for decades to come and increase the range of studies for which the species is employed. Marmosets, for example, are an attractive species for studying diseases with a developmental component because of a fast life cycle and high reproduction rates. The rapid sexual maturation of marmosets (18 months) will be critical for studying schizophrenia, autism-spectrum disorders, and attention-deficit hyperactivity disorder in which psychopathology is manifest in childhood. Furthermore, visual deficits, particularly in the M pathway of early vision are well documented in schizophrenia and can be studied in marmosets as well as studying oculomotor, face processing, and visual attention deficits in autism. Marmosets are the shortest-lived anthropoid primates, with a typical lifespan of 9–12 years as compared with 25–40 years for rhesus macaques. Their shorter lifespan makes them better suited to longitudinal studies of age-related vision loss. Finally, an acute need exists throughout neuroscience for means of targeting the elements of cortical circuits in the non-human primate. The benefits of the development of these capacities, both through the establishment of genetically engineered Cre and Flp lines and through the development of enhanced viral targeting capacities (11) will be particularly impactful in the visual system due to the over 50 years of foundational research on visual circuits.

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