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REVIEW

USING RATS FOR VISION RESEARCH

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Abstract—A wide variety of species are used for the study of visual neuroscience. This is beneficial because fundamental mechanisms and theoretical principles of vision are likely to be highly conserved, while different species exhibit different visual capacities and present different technical advantages for experiments. Eight years ago my laboratory adopted the hooded rat as our primary preparation for vision research. To some this may be surprising, as nocturnal rodents have often been presumed to have poor vision and weak visual behavior. This commentary will provide my personal perspective on how I came to work with rats; discuss an example research project for which rats have been advantageous; and comment on the opportunities and challenges of the preparation.

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Key words: rodent vision, visual behavior, pigmented rat, visual psychophysics.

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INTRODUCTION

The development of the visually behaving macaque model revolutionized visual neuroscience, allowing neurophysiology to be directly linked with behavior on a trial-by-trial basis. Immense progress has been made in this preparation, and we expect it will remain the best or only preparation for many visual studies. Several powerful methods are difficult or costly to perform in animals with such large brains, however, including lesions, slice physiology, recording or imaging simultaneously from multiple visual areas, filling and reconstructing individual cells, anatomic tracing of long-range projections, genetic labeling of specific cell types, isolating mutants, transgenic animals, or comparisons across large populations of individuals. Accordingly, these methods are rarely employed in macaque vision research, leaving gaps in our knowledge. Therefore a small mammal with robust visual behavior would be valuable for our research and for the field in general.

HOW WE CHOSE RATS

We considered a wide range of small mammal species, and commenced pilot studies of visual behavior of candidate species until a suitable preparation was identified. In choosing candidates we considered visual characteristics (prominence of visual system; percent of photoreceptors that are cones), experimental accessibility (suitability for optical imaging, slice preparation, behavioral tractability), pragmatic factors (size, availability, cost, maintenance burden, epizootic problems, ease of handling), and research infrastructure (existence of breeding colony, stereotaxic atlas, genome sequence, genetic libraries), to the extent that these facts were known. No species was ideal in all respects. Balancing the advantages and disadvantages in different ways, our top candidates were California ground squirrel, degu, gerbil, guinea pig, rat, and mouse. Our short list also included thirteen-lined ground squirrel, Nile rat, hamster, tree shrew, ferret, and bush baby. We began by testing four candidates. Two were chosen for highly developed, cone-dominated visual systems, in spite of limited research infrastructure: California ground squirrel (*Otospermophilus beecheyi*) and degu (*Octodon degus*). Two were chosen for highly developed infrastructure, in spite of limited visual systems: rat (*Rattus norvegicus*, specifically the pigmented Long-Evans strain), and mouse (*Mus musculus*, specifically the F1 hybrid of c57bl/6 $\times$ dba/2).

The goal was to find one small mammal that could learn a visual task by operant conditioning with two-alternative forced choice (2AFC) trial design (rather than go–nogo), appetitive reward (as against negative reinforcement, e.g., escaping water), liquid reward (as against food pellets), and computer-displayed visual

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Abbreviation: 2AFC, two-alternative forced choice.

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stimuli (as against physical objects or cue cards). In these respects, we mimicked conditions typical of human and monkey visual behavior experiments, which are well suited to providing a large number of trials in rapid succession with temporal precision and minimal human intervention.

Our pilot task was discrimination of high-contrast low-spatial frequency sinusoidal gratings at mesopic mean luminance. We used an operant chamber that had been previously developed for 2AFC olfactory and auditory tasks in freely behaving rats (Uchida and Mainen, 2003; Hromádka and Zador, 2007; Otazu et al., 2009). For control of visual stimuli, trials, and training we used an early prototype of the training protocols and custom software that were further developed and described in detail elsewhere (Meier et al., 2011, and supplementary materials thereof). In the pilot study trials were initiated by insertion of nose in the center nose poke, and terminated by response at either the left or right nose poke. Correct responses earned liquid reward; incorrect responses earned a brief penalty time-out during which a flickering checkerboard was displayed (see Supplemental Videos 1 and 2).

The first species we succeeded in training were Long-Evans hooded rats (Fig. 1A, B; Supplementary Video 1) and California Ground Squirrels (Fig. 1C, D; Supplementary Video 2). The rats we tested were young adults (P30–P90). The squirrels we tested were captive-raised 1-year-old adults, born of wild-caught pregnant mothers. The epizootic risks necessitated BL2 handling, off-site housing, and daily transportation by car to the testing laboratory. Despite these sub-optimal conditions the squirrels learned rapidly and performed well in the task. In our initial pilot, neither mice nor degus learned the visual task. We chose to proceed with rats rather than squirrels because rats were able to learn and perform all the visual tasks we needed, and the existing research infrastructure for rats is far better than for squirrels. With further effort, protocols have since been optimized for freely behaving mice as well (for preliminary report, see Sriram et al., 2013). We abandoned efforts to optimize protocols for degus, and did not test the other candidate species, so their visual and behavioral capacities in our task remain unknown.

Using rats as our primary preparation, we developed software, hardware, and operant chambers for automated training and testing of rodents in visual tasks (Meier et al., 2011). The ability to train a large number of subjects in a compact space is one significant advantage of using a small mammal model. We note that other groups had previously (Birch and Jacobs, 1979; Cowey and Franzini, 1979; Keller et al., 2000; Prusky et al., 2000) or contemporaneously (Douglas et al., 2006; Minini and Jeffery, 2006; Bussey et al., 2008; Zoccolan et al., 2009) developed related methods for training and testing vision in rodents, and new methods are emerging daily, especially for mice (e.g., Chen et al., 2008; Harvey et al., 2009; Andermann et al., 2010; Dombeck et al., 2010; Niell and Stryker, 2010; Busse et al., 2011; Harvey et al., 2012; Histed et al., 2012).

AN EXAMPLE STUDY USING RATS

We find rats to be excellent subjects for studies that require complex visual behaviors and large numbers of trials from multiple subjects. To illustrate this, consider our use of rats to study spatial context effects (Meier et al., 2011; Meier and Reinagel 2011; Meier and Reinagel 2013). A question of broad interest in vision research is to understand how spatially proximal visual

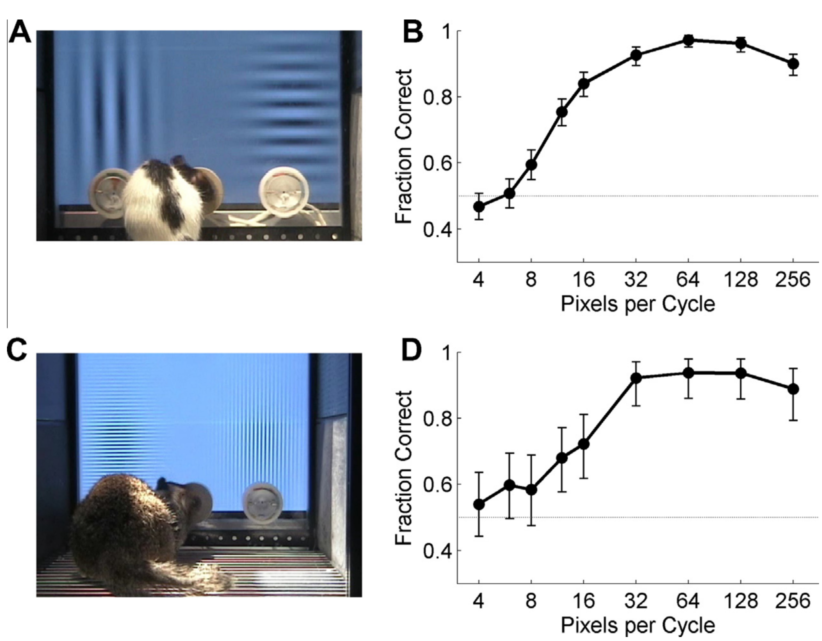

Fig. 1. Small animals tested for visual behavior. (A) Long-Evans hooded rat in pilot test, performing 2AFC orientation discrimination. (B) Performance of one of the rats as a function of spatial frequency (8437 trials over 18 days). (C) California Ground Squirrel in pilot test, performing 2AFC orientation discrimination. (D) Performance of one of the squirrels as a function of spatial frequency (797 trials over 2 days). Mice and *Octodon degus* were also tested, but performed poorly under the pilot test conditions.