GCaMP8 transgenic mice learn to make visual decisions

Olena Didenko, Sandra Tan, Huriye Atilgan, Armin Lak
Department of Physiology, Anatomy & Genetics, University of Oxford, Oxford UK
Correspondence: armin.lak@dpag.ox.ac.uk

Abstract
Transgenic mice engineered to express calcium indicators such as GCaMP have revolutionized exploration of neuronal circuit function. The latest development, GCaMP8 transgenic mice, exhibits enhanced temporal kinetics and sensitivity of neural signals, opening new avenues for studying neuronal dynamics within behaviorally relevant time frames. However, in initial attempts, it has been chalenging to train these mice in visual decision making tasks. Here we show that GCaMP8 transgenic mice, specifically TetO-jGCaMP8s x CaMK2a-tTA mice, learn to perform head-fixed visual decision tasks with a rate and accuracy comparable to wildtype mice. These proof-of-principle results enhance the utility of these transgenic animals in neuroscientific studies of learning and decision making.

Introduction
The latest development of GCaMP8 transgenic mice exhibits ultra-fast temporal kinetics suitable for studying behaviorally relevant neuronal dynamics[1]. However, in initial attempts, it has been chalenging to train these mice in visual decision making tasks[2]. Here we report that TetO-jGCaMP8s (Jax: #037717) x CaMK2a-tTA (Jax: #007004) mice can learn to perform a standardized head-fixed visual decision task[3,4] (Fig.1a), following a training protocol we described recently[5].

Methods
Animals underwent headplate implantation surgery to secure a head fixation device on the skull. Water restriction and behavioral training started at least 5 days after the surgery. Water-restricted animals were acclimatized to head fixation for at least 3 days, and then trained in the detection task. After the mice kept the wheel still for at least 0.7 to 0.8 seconds, a sinusoidal grating stimulus of varying contrast appeared on either the left or right side of the screen (±35° azimuth, 0° altitude). Concomitant to the appearance of the visual stimulus, a brief tone was played to indicate that the trial had started (0.1 s, 5 kHz). Mice were able to move the grating stimulus on the monitor by turning a wheel located beneath their forepaws. If mice correctly moved the stimulus 35° to the center of the screen, they immediately received a water reward (3 uL). Conversely, if mice incorrectly moved the stimulus 35° towards the periphery, or failed to reach either threshold within 60 seconds, a noise burst was played for 0.5 seconds followed by a timeout of 2 seconds. In the initial training days, only high contrast (100%) stimuli were presented. Stimuli with lower contrasts were gradually introduced after mice exhibited sufficiently high performance on 100%-contrast trials (>70% correct). During this training period, incorrect responses on high contrast trials were followed by 'repeat' trials, in which the previous stimulus location was repeated.

Results
The transgenic mice learned the task well, showing steeper psychometric curves as learning progressed (Fig.1b,c). The animals reached an accuracy of above 75% after, on average, 14 days of training, comparable to wildtype mice trained on the same task[3,4]. After reaching expert behavior, mice had stable daily psychometric curves, performing an average of 340 trials per day with accuracy rate of 80-95%. Moreover, the transgenic mice stably maintained body weights of at least 85% of pre-water control body weight, and did not show any visible sign of distress.

Discussion
These results indicate that TetO-jGCaMP8s x CaMK2a-tTA mice can perform head-fixed visual decision tasks with high accuracy, enhancing their utility in neuroscientific studies of learning and decision making.

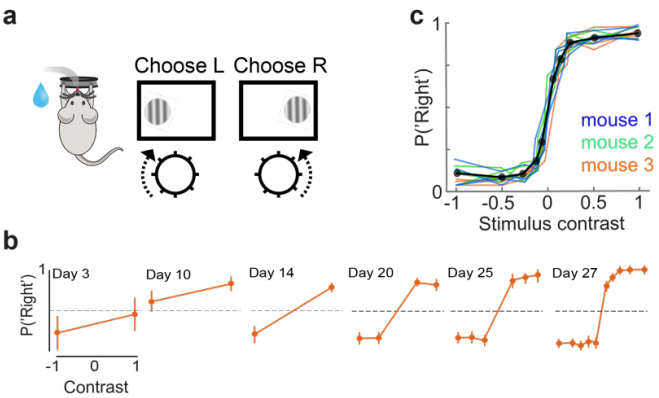

Figure 1. Behavioral task setup and learning curves in GCaMP8 transgenic mice.
a) Illustration of the two-alternative visual decision task. b) Psychometric curves across example training days for a representative mouse. c) Final four session psychometric curves for three GCaMP8 transgenic mice, and their average curve (black).

References:
1. Zhang, Y., et al (2023) Fast and sensitive GCaMP calcium indicators for imaging neural populations. Nature.
2. Wang, T., et al (2023) jGCaMP8 transgenic mice. Janelia Research Campus. https://doi.org/10.25378/janelia.24565837.v3
3. Burgess C., et al (2017) High-yield methods for accurate two-alternative visual psychophysics in head-fixed mice. Cell Reports.
4. IBL (2020) Standardized and reproducible measurement of decision-making in mice. eLife.
5. Frtische, M. et al (2023) Temporal regularities shape perceptual decisions and striatal dopamine signals. bioRxiv.
Acknowledgements: Wellcome Trust (213465/Z/18/Z) and ERC (underwritten by UKRI, EP/X026655/1).