Moving from Cellular Responsiveness to Functional Vision: Characterizing the Perceptual Performance of Optogenetic Vision

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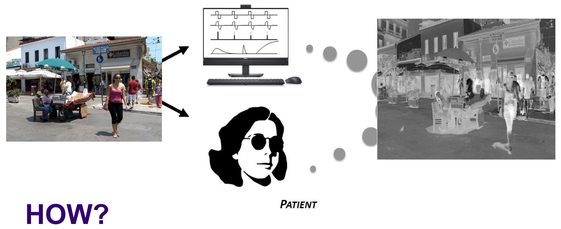
1. The Virtual Patient

Predicting the Perceptual Experience of Optogenetic Vision

- Optogenetic sight recovery uses retinaldehyde-binding proteins to elicit light sensitivity in remaining healthy retinal cells (bipolar and/or ganglion cells) of patients with inherited retinal disorders.
- **How do we predict functional vision from cell responsiveness?**
- Here, we simulate a virtual patient to predict the perceptual performance of optogenetic vision.



HOW?

1. **Model the neural response of opto-protein $^{4x}BGAG_{12,460}$:SNAP-mGluR2 [2]**
2. **Measure visual acuity of simulated optogenetics**
   - **2.1 Metric:** Temporal Contrast Sensitivity Function (TCSF)
   - **2.2 Experiment:** To identify orientation (+/- 45°) of gratings across a range of spatial (0.5 - 36 Hz) and temporal frequencies (3 - 30Hz)
   - **2.3 Conditions:** tCSFs were measured for (i) neurotypical vision and (ii) optogenetic filtering

2. Modeling the Optogenetic Response

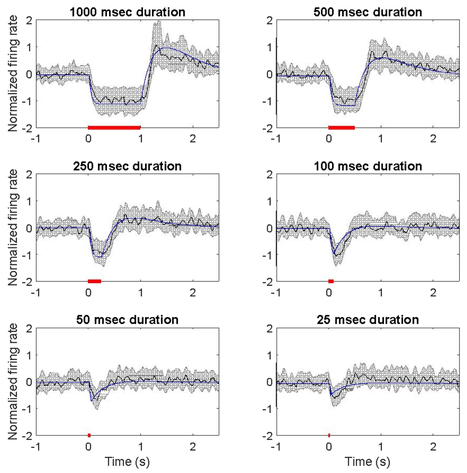


Fig.1. (i) Average RGC responses (black) (ii) model predictions (blue) for flashes of light with varying durations (red).

- We used the following system of differential equations to model neural response time courses to flashes of light in rd1 mice retina expressing $^{4x}BGAG_{12,460}$:SNAP-mGluR2 [2].
- Photoactivation of this opsin in retinal ganglion cells (RGC) triggers a fast suppression of spontaneous firing followed by a rebound excitation when light is turned off.

$$\frac{dy_{on}}{dt} = \frac{-aS + (b_0 - y)}{\tau_{on}}$$

$$\frac{dy_{off}}{dt} = \frac{-aS + s(b - y)}{\tau_{off}}$$

$$\frac{db}{dt} = \frac{abS + (b_0 - b)}{\tau_b}$$

S(t): stimulus
Y(t): firing rate
b(t): drifting baseline

a,b : scale factors
b0 : starting baseline
τ_{on}, τ_{off}: time constants

3. Measuring Visual Acuity: Simulated Optogenetics

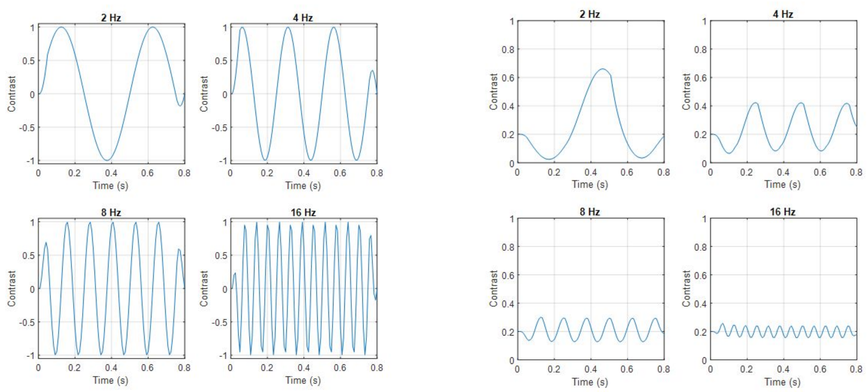


Fig 2. Modulation of sinusoidal stimuli by optogenetic filtering through $^{4x}BGAG_{12,460}$:SNAP-mGluR2

- Change in shape of the sinusoid due to non-linear photokinetics of the opsin
- Reduction in contrast predicts a loss of sensitivity

4. TCSF Detection Thresholds

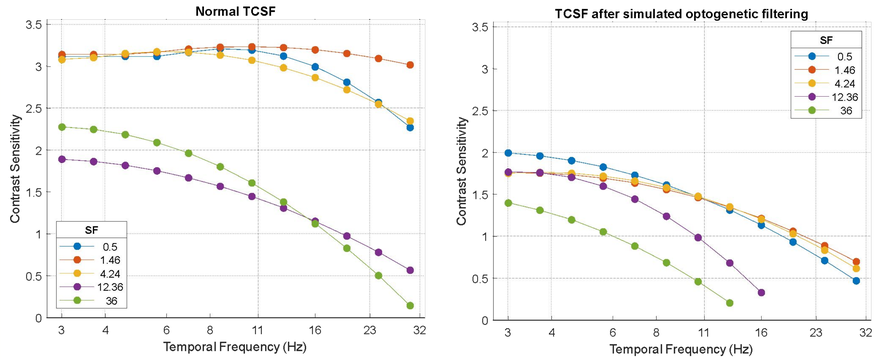


Fig 3. Temporal contrast sensitivity for varying temporal and spatial frequencies averaged across five participants with (i) neurotypical vision (ii) optogenetic vision based on the model for $^{4x}BGAG_{12,460}$:SNAP-mGluR2 opsin.

5. Discussion

- **Sensitivity:** tCSF measurements indicate **10x fold loss in sensitivity** - even more severe at higher temporal frequencies (Fig. 3).
- **Snellen Acuity: ~20/40** at low temporal frequencies to **~20/100 - 20/200** at high temporal frequencies.
- **Target population:** patients with **uncontrollable nystagmus** might be **poor candidates** for optogenetic treatments. Losses are likely to be **more severe in the presence of rapid eye-movements**
- **Applicability:** Framework can be extended to model any opto-protein; provides a systematic quantitative methodology to study perceptual performance

REFERENCES
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[2] Holt et al. 2022. Restoration of high-sensitivity and adapting vision with a cone opsin. Nature Communications (DOI: https://doi.org/10.1101/2022.04.07.487476)
[3] Fine, Boynton 2015. Pulse trains to percepts: The challenge of creating a perceptually intelligible world with sight recovery technologies. Philosophical Transactions of The Royal Society B Biological Sciences. (DOI: 10.1098/rstb.2014.0208)

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