

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

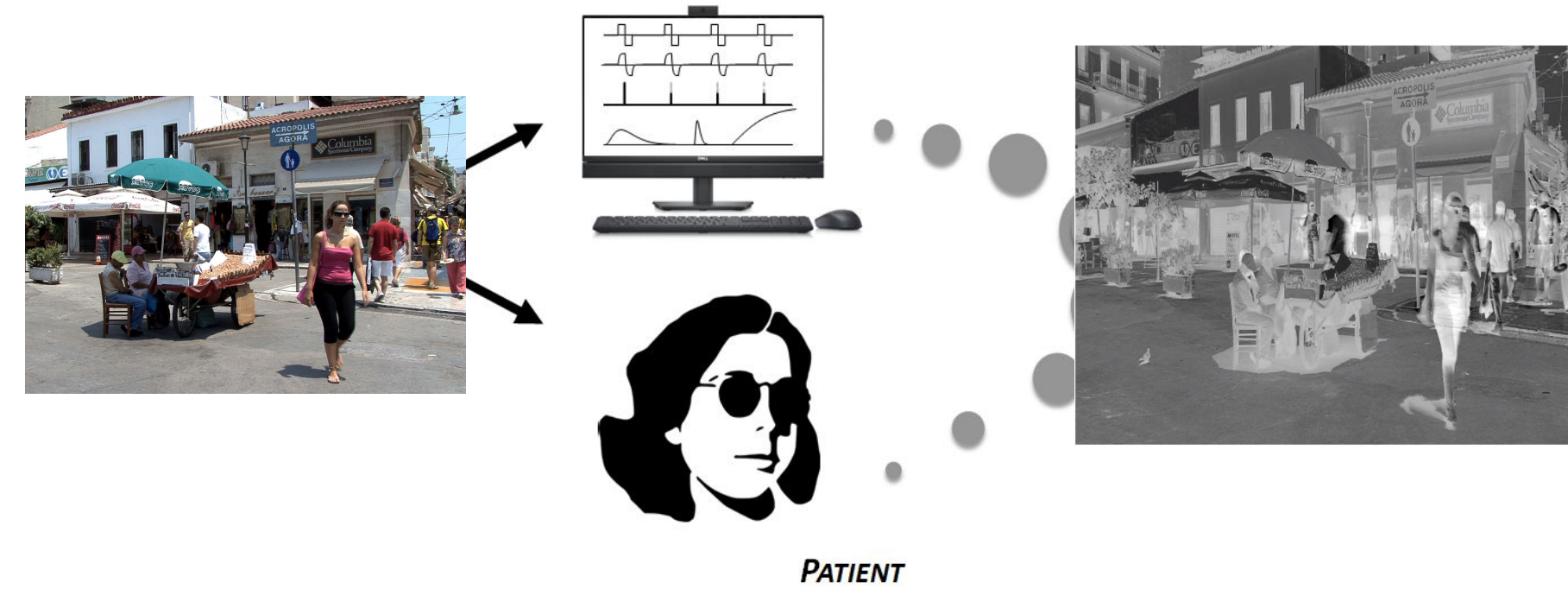
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## 1. The Virtual Patient

### 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.



1. Model the neural response of opto-protein  $4\times\text{BGAG}_{12,460}:\text{SNAP-mGluR2}$  [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

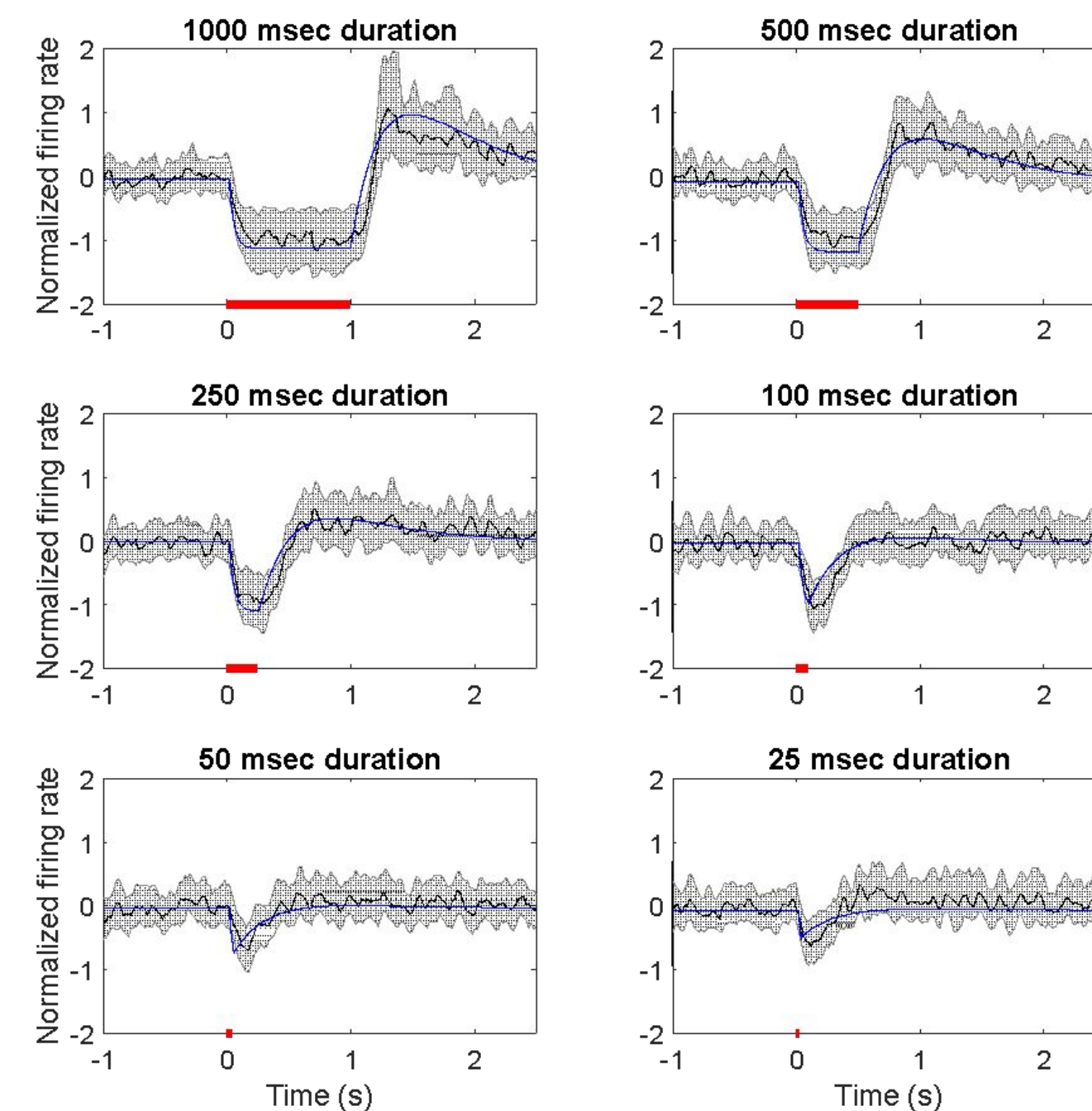


Fig.1. (i) Average RGC responses (black) (ii) model predictions (blue) for flashes of light with varying durations (red).

- We used the following system of differential equations to model neural response time courses to flashes of light in rd1 mice retina expressing  $4\times\text{BGAG}_{12,460}:\text{SNAP-mGluR2}$  [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.

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

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

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

$a, b$ : scale factors  
 $b_0$ : starting baseline  
 $\tau_{on}, \tau_{off}$ : time constants

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

## 3. Measuring Visual Acuity: Simulated Optogenetics

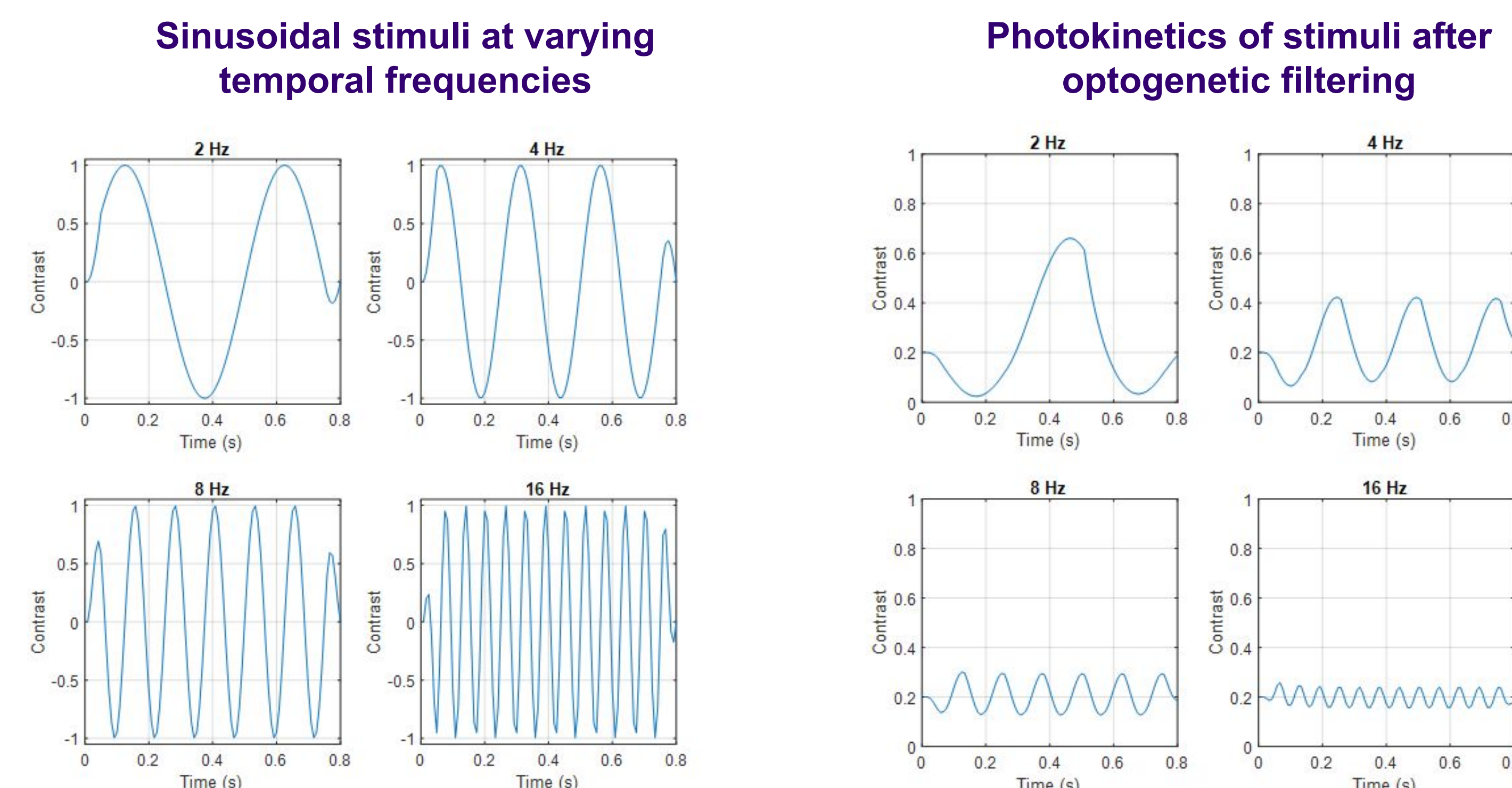


Fig 2. Modulation of sinusoidal stimuli by optogenetic filtering through  $4\times\text{BGAG}_{12,460}:\text{SNAP-mGluR2}$

- 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

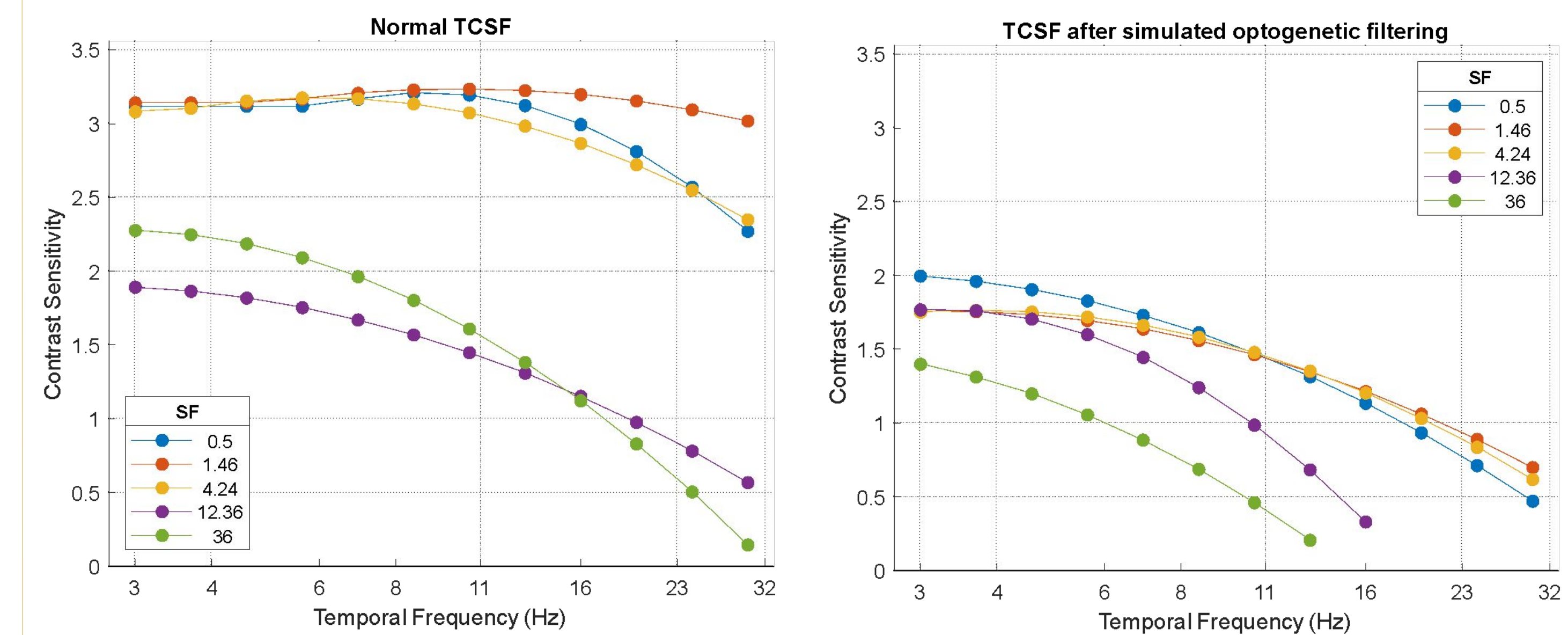


Fig 3. Temporal contrast sensitivity for varying temporal and spatial frequencies averaged across five participants with (i) neurotypical vision (ii) optogenetic vision based on the model for  $4\times\text{BGAG}_{12,460}:\text{SNAP-mGluR2}$  opsin.

## 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)

### ACKNOWLEDGEMENTS

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