High-resolution VSDI retinotopic mapping via a DLP-based projection system

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Abstract: High-resolution recording of visual cortex activity is an important tool for vision research. Using a customized digital mirror device (DMD) - based system equipped with retinal imaging, we projected visual stimuli directly on the rat retina and recorded cortical responses by voltage-sensitive dye imaging. We obtained robust cortical responses and generated high-resolution retinotopic maps at an unprecedented retinal resolution of 4.6 degrees in the field of view, while further distinguishing between normal and pathological retinal areas. This system is a useful tool for studying the cortical response to localized retinal stimulation and may shed light on various cortical plasticity processes.

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1. Introduction

Recording the population response of the visual cortex is of great importance for studying basic visual processing, plasticity processes, and various pathologies. Of particular interest to this study is the generation of retinotopic maps, which can shed light on many retina-visual cortex processes, as well as plasticity, and circuitry [1–4]. Various techniques are available, enabling the investigation of the cortical population response; one such technique is Voltage-sensitive dye imaging (VSDI). VSDI is an optical imaging technique based on the binding of voltage-sensitive dye molecules to the neuronal membrane [5]. The dye molecules convert changes in the membrane potential into changes in the emitted fluorescence [6,7], which is detected by an optical system. This technique enables the high-spatial and temporal resolution imaging of the cortex in general [8,9] and is widely used for studying the visual cortex in primates [10–13], cats [14,15], and rodents [3,16]. For most of the electrophysiological methods used for vision research, visual stimulation is performed with a computer monitor [17] or a back-projection screen [18], which allows an easy and affordable method to project large visual field stimuli. However, these techniques have several limitations. First, since most of these studies are performed on anesthetized animals, it is difficult to control for fixation and to present the stimulus at a specific retinal location. Second, it is difficult to control for eye movements. Third delivering high powered light for optogenetic stimulation [19] or for retinal prostheses stimulation [20,21] is challenging. Finally, these approaches rely on the optical system of the rodent, which is known to introduce a large amount of aberration to the image [22,23], thus degrading the visual function and electrophysiological responses [24]. To overcome the limitations of the available systems, we developed a unique projection system based on a slit lamp equipped with a Digital Micromirror Device - Digital Light Processing (DMD-DLP), which enables an accurate projection of patterns on a desired region. DMD-DLP enables the projection of flexible stimulation patterns at high spatio-temporal resolution. The position of the projected pattern is monitored through a CCD camera, which facilitates the control and validation of the position of the retinal stimulation. The
DLP system offers great flexibility and facilitates the generation and projection of visual stimuli at varying intensities and spatial frequencies (Fig. 1).

Fig. 1. An illustration of the experimental set-up, consisting of a DLP-DMD-based projection system, a retinal imaging system, and an optical imager for recording cortical activity. The pattern generated by the DLP-DMD projector is reflected through a mirror to a set of lenses (L1, Fig. 1) consisting of a Plano concave and doublet lens to achieve convergence. The converged pattern is then projected onto the rat retina through a mirror M2. The location of the stimulus on the retina is then imaged using a zoom lens (L2) and a CCD camera. Cortical activity is imaged by a CMOS camera situated above the animal and a mounted tandem lens, 85 mm f/1.4 lens and a 50mm f/1.2. See more details in the Methods section.

Using the stimulation and imaging systems, we show here the response of the rodent visual cortex to visual stimuli at various intensities and spatial frequencies while creating retinotopic mapping at an unprecedented resolution of 4.6 visual degrees.

2. Methods

2.1. Animals & anesthesia

All experimental and surgical procedures were approved by the Bar-Ilan University Ethics Committee [04-01-2017] for animal research and were carried out in accordance with the National Institutes of Health guide for the care and use of Laboratory animals. We used 23 male and female 8-12-week-old (200-250 grams) Long Evans rats. Animals were initially subcutaneously injected with Domitor (Medetomidine hydrochloride 1 mg/ml; 0.3 mg/100 g body weight, Orion Pharma, Finland) and put on isoflurane inhalation (1.2 ml/hr), with a periodic addition of half the initial Domitor dose every two hours. The animals’ temperature was maintained throughout the experiment (36.5-37.5°C) with a homeothermic blanket, controlled through feedback from a rectal probe.
2.2. Surgical procedure and voltage sensitive dye staining

Following Domitor and Isoflurane-induced anesthesia, the animals were head-fixed and the skin above the skull was removed with scissors and soothed with Lidocaine (Lidocaine HCl 200 mg/10 ml, Rafa Laboratories). A custom-made steel chamber was attached to the skull above the right primary visual cortex (V1), while the center of the chamber, located 7 mm posterior and 2.75 mm lateral to bregma \cite{25,26} was attached with dental cement (GC Relin, GC America, Inc., Alsip, IL 60803 USA). Following the attachment of the chamber, a craniotomy was performed, and the dura was gently removed to expose V1. The brain tissue was nourished throughout the entire procedure by replenishing the chamber with Artificial Cerebro-Spinal Fluid (ACSF), which was adjusted to a pH of 7.4 ± 0.1. After the V1 cortex was exposed, a mixture of ACSF and a voltage-sensitive dye (RH2080 1 mg/ml; Optical Imaging, Rehovot, Israel) was placed above the cortex. The dye was washed and replaced every 20 minutes for 2 hours to ensure optimal staining. Following the staining procedure, lukewarm agar (Agarose, low gelling temperature; SIGMA-Aldrich, USA) was poured into the chamber and then sealed with a microscope cover glass for optimal optical transmission. The animal head was then fixed to the imaging set-up using the customized chamber.

2.3. Visual stimulation

For visual stimulation we used a costume-built projection system (EKB, Ramat-Gan, Israel) based on a slit lamp apparatus. The system consists of a DLP-DMD projector (DLP LightCrafter 4500, Texas Instruments, Inc., Dallas, TX, USA) controlled by software and passive optical elements that projected an image onto the retina of the rat (Fig. 1). The projector used a green LED (\(\lambda=520\) nm) and a DMD mirrors array (1024 by 768) to shape the image as desired. The desired pattern was reflected through a mirror (PF40-03-P01, Thorlabs)-M1 Fig. 1. The reflected rays were then relayed through a set of lenses (L1, Fig. 1) consisting of a Plano concave (L-PCX388, Thorlabs, \(f=300\) mm) and doublet lens (L-AOC307, Thorlabs) to achieve convergence and a desired image size on the retina. Finally, the relayed image from these set of lenses is reflected through a custom-made mirror (M2, Fig. 1) to the rat retina. This mirror has two holes to enable the imaging of the pattern on the retina (see next paragraph for details). The images were created by MATLAB (The MathWorks, Inc., Natick, MA, USA), uploaded and stored in the projector’s flash memory for efficient extraction. The image’s sequence/order of projection and timing were controlled by the projector’s software (Light Crafter). For our experiments we used four types of stimuli/images (Visualization 1): 1) 1.3*0.8 mm solid square green stimuli presented for 20 ms at a rate of 1 Hz with three different intensities: 140 nW/mm², 670 nW/mm², and 1060 nW/mm² (Fig. 2); 2) alternating gratings (47% contrast, Fig. 3(A)) presented at 1.6, 3.3, 6.7 and 13.4 cycles per millimeter (cpm) (350 nW/mm²); 3) a 1.3*0.8 cm rectangle divided into 4 quadrants (Fig. 4(A)), with an interleaving presentation, at an intensity of 111 nW/mm² at either the nasal or the temporal retina; and 4) a grid of 8 stimuli at a diagonal distance of 270 µm with an interleaving presentation at 1 Hz (Fig. 5(A)). To project the stimulus on the retina, pupils were dilated with Hydramide (Tropicamide 0.5%, Fisher Pharmaceutical, Ltd) and Efrin-10 drops (Phenylephrine HCL 10%, Fisher Pharmaceutical, Ltd) and a microscope cover glass (d = 13 mm) was mounted on the eye coupled by an ophthalmic gel (Ocu+, CIMA Technology, Inc., Pittsburgh, PA USA), to achieve refractive index matching at the interface between the cornea and air and thus enable the imaging of the retina at the back of the eye. Real-time imaging of the retinal stimulus was performed by a camera (DMK 33GP1300, The Imaging Source, Bremen, Germany), in front of which is a zoom lens (VS-LD75 f = 73.98, F# = 3.8, Vital Vision Technology Singapore) which enables one to position and focus the stimulus on the retina at a desired location with high precision (Fig. 1, L2). The focus was obtained by adjusting the distance between the zoom lens and the animal cornea.
2.4. Image acquisition

To record the fluorescence changes in the visual cortex, we used an upright microscope with a 12-V halogen lamp gated by a Uniblitz shutter and controlled by Optical Imaging 3001 VDAQ software (Optical Imaging, Rehovot, Israel). The cortex was excited by a 630 nm light and the emitted fluorescence was collected at 665 nm and captured by a high-resolution CMOS camera (Photonfocus, Switzerland, 12 bit) at a rate of 100 Hz and 1080 by a 1308 pixels. This resulted in a frame size of 5.39 mm by 6.53 mm of the brain (~200 pixels/mm). For easy storage and manipulation, the frames were spatially down-sampled by a factor of 4, resulting in a resolution of ~50 pixels/mm (around 20 μm resolution, higher than the 50 μm resolution usually reported for cortical recordings [5]). Each experiment consisted of from 10 to 20 repetitions of 10 sec recording time (1000 frames). For baseline, we used the first second of the recording, where no stimulus was presented. The stimuli were then presented for 9 seconds while cortical responses were recorded and analyzed as described below.

2.5. Data analysis

Data were averaged and a detrend was performed using a two-part exponential fit to the data [27] to remove the fluorescence decay. The DF/F of each pixel was then calculated by subtracting and then dividing the exponential fit from each pixel value. To convert the DF/F to Z-score values, the DF/F values were divided by the standard deviation of the first second DF/F, which served as a baseline. We refer to the calculated Z-score values as STD as they represent a normalization of the Standard Deviation. The data were filtered for each condition both temporally (10 Hz lowpass filter) and spatially (Gaussian filter). Once smoothed, we isolated the waveforms arising from the stimuli using a multi-parametric thresholding method, which extracted the pixels that contributed most to the response elicited by the stimulus. Specifically, using MATLAB functions we calculated the peak amplitude and time to rise and settle parameters for these values for each pixel. To generate the retinotopic maps, we applied several criteria for each pixel: First, we isolated the 1-3 percent of the pixels with the highest peak amplitude and thresholded the peak amplitude at a time window of 150-300 ms. We then further selected pixels that returned to baseline within 1 second from the stimulus. Next, we determined the center of activity (COA) by applying a spatial Gaussian filter (5 pixels = 1 Standard Deviation) and choosing by the pixel with the resulting maximal amplitude.

2.6. Retinal laser lesions

To study the ability of the system to distinguish between normal and pathological retinal areas, 2 mm lesions were induced in the temporal retina using a 532 nm coagulating laser (MERDIAN, λ\text{\textit{t}}=532\text{\textit{nm}}) at a 250msec pulse width and a 100 mW intensity.

2.7. Calculation of the cortical magnification factor

The CMF was calculated similarly to previous reports [25,28]. In short, for two Centers of Activity (COA) in V1, each corresponding to the response to a different visual stimulus, the cortical magnification is defined as the distance (μm) between the two COA divided by the angle (degrees) between the two stimuli locations in the visual field. Since we presented the stimulus directly on the retina, we converted the retinal distance to visual degrees according to the rat nodal point distance of 3.3 mm [22], where 59 μm on the retina correspond to 1 degree in the visual field.
3. Results

3.1. Responses to stimuli with various irradiances

We presented 20ms flashes at a rate of 1Hz with 3 increasing irradiances (140, 670, and 1060nW/mm$^2$) with a stimulus size of 1.3mm*0.8mm (corresponding to 22*13.5 degrees in the rat visual field). Figure 2(A) presents the DF/F curve in the center of activity in response to flashes with increasing irradiances. Figure 2(B) presents the maximal amplitude versus light intensity (error bars SE, n = 12), showing an increase in the response amplitude with increasing stimulus irradiance with the response saturating at stimulus irradiances higher than 1000nW/mm$^2$. An increase in stimulus irradiance was accompanied with only a small decrease in the response latency (Fig. 2(C)) and a slower decay, compared with the rising phase, probably because it reflects a population response [29], where neurons farther away from the center of activity are activated later, thus slowing down the decay phase. Figure 2(D) presents an example of the spatial spread of the response for the same experiment presented in 2A. The response was observed in the V1 visual cortex and increased in amplitude with increasing irradiance, reaching a 0.18% fractional amplitude (6*STD) for the highest intensity level. More importantly, the increase in flash irradiance was associated with a larger spread of the response throughout V1, which reached the extrastriate area (lateral side) with the highest irradiance. In contrast, the lowest flash intensity maintains a localized response with low amplitude. The extrastriate responses were not analyzed further here.

3.2. Response to alternating gratings

To investigate the spatial function of the visual system, we projected alternating gratings with increasing spatial frequency (1.6, 3.3, 6.7 and 13.4 cycles per millimeter, CPM), as shown in Fig. 3(A). The gratings were presented at 1-2Hz with increasing and decreasing spatial frequency order (Visualization 1). A decrease in the response with increasing spatial frequency is shown in a characteristic example in Fig. 3(B). Figure 3(C) presents the average and standard error bars of the fractional response amplitude for the three presented spatial gratings (n = 8, except for 13.4cpm where n = 2, Standard Error bars). The cortical responses declined with increasing stimulus spatial frequency, reaching the noise level at about 16CPM.

3.3. Retinotopic mapping

To investigate the retinotopic structure of the response, we presented quadrants of a rectangle (each quadrant size was 660µm horizontally by 410µm vertically, corresponding to 11.3*7.1 degrees in the rat visual field). Using real-time retinal imaging, we applied the stimuli either nasally or temporally to the optic nerve (Fig. 4(A)) at a rate of 1Hz. To obtain a retinotopic map, amplitude and latency thresholds were applied to the response (Fig. 4(B)) and highlighted the active pixels for each stimulus (Fig. 4(B)). Moving the retinal stimuli temporally and superiorly, the cortical responses center of activity moved anteriorly and laterally, respectively (Fig. 4(C)). Figure 4(D) presents a combination of responses to the nasal and temporal retina, showing a clear geometric organization where the responses to the nasal retinal stimulation (corresponding to the temporal visual field) appeared in the medial-posterior area of V1 and the temporal retinal (nasal field) responses appeared in the lateral-anterior area of V1, in agreement with previous reports [25,30]. Figure 4(E) shows the two groups of cortical activations at a higher magnification.

3.4. High resolution retinotopy

Following the robust response obtained for the four 660µm *410µm stimuli (as mentioned in the previous section), we stimulated the retina at an even higher resolution with 8 stimuli, separated diagonally at a distance of 270µm (which corresponds to 4.6 degrees) (Fig. 5(A)). The stimuli were presented at a rate of 1 Hz. The obtained responses reached a peak at between
Fig. 2. Cortical activity in response to flash stimuli with increasing irradiance. A. Cortical responses to a flash (10 ms, 1 Hz) stimulus of 22°13.5 degrees in the visual field, with increasing irradiance. B. Increased amplitude of responses (DF/F) as a function of increasing irradiances (n = 12, data points were fitted with a saturation function). C. Implicit time as a function of irradiance. D. Characteristic cortical responses showing increased spreading of the response with increasing stimulus irradiance (the diamond marker represent the center of activity). A = anterior, L = lateral, P = posterior, M = medial.
Fig. 3. Cortical responses to alternating bar stimuli with increasing spatial frequency. A. Retinal imaging of grating stimulus projected on the retina at four spatial frequencies. B. Characteristic responses obtained for the four alternating grating spatial frequencies. C. Decreased amplitude responses as a function of increased spatial frequency (Error Bars are SE, Noise level = 2*STD).

200 and 300 msec after the stimulus with an amplitude of 3 to 6 standard deviations (Fig. 5(B)). Figure 5(C) shows the localized response to each of the stimuli, where the center of the response activity shifted laterally and anteriorly with the stimulus shifting temporally. The combination of the cortical responses to the eight stimuli generated retinotopic mapping: the nasal retinal stimuli elicited responses at the medial-posterior area of V1, whereas temporal retinal stimuli elicited responses at the lateral-anterior area of V1 (Fig. 5(D)), in agreement with previous studies [25,30]. Figure 5(E) presents the center of activity of the responses, showing a preserved retinotopy. Overall, the average cortical magnification factor (CMF) found for the responses was 35.3 (STD = 25.3) µm/deg, similarly to Gias et al. [25].

3.5. Imaging a retinal laser-induced scotoma

To demonstrate the ability of our system to differentiate between specific retinal regions with and without pathologies, we performed a laser lesion (about 2 mm in diameter) on the temporal retina (Fig. 6(A), right). We then positioned the 8-locations stimulus as described above with the 3 most temporal locations projected on the retinal laser lesion (Fig. 6(A), left). Representative waveforms (after applying an amplitude threshold and temporal limiting) are presented in Fig. 6(C). The stimuli located on healthy retinal regions resulted in robust (5-7 SD) and localized responses (Fig. 6(C) & (D), whereas the stimuli located on the retinal laser lesion did not elicit any
3.4 High Resolution Retinotopic Mapping

Following the previous section, we present the high resolution retinotopic mapping results. Figure 4 illustrates the mapping from nasal and temporal retinal stimuli to a 660µm*410µm rectangle stimulus (corresponding to 11.3*7.1 degrees in the rat’s visual field). A. The location of the eight stimuli in the nasal and temporal retina. S = superior, T = temporal, I = inferior, N = nasal. B. Characteristic responses of the visual cortex to each retinal stimulus. C. The location of cortical activation obtained for each stimulus after applying a gaussian filter. D. Combined retinotopic mapping generated from visual cortex activity recorded in response to the nasal and temporal retinal stimuli shows a clear organization. Each color represents the location of the response to the matched retinal stimulus (presented in diamond shapes with each color corresponding to a different location). E. The center of activation of each of the responses is shown in a larger magnification. A = anterior, L = lateral, P = posterior, M = medial.
Fig. 5. High-resolution retinotopy. A. The position of the eight retinal stimuli is shown in real retinal imaging (left, green was added for image clarity) and illustrated (right). S = superior, T = temporal, I = inferior, N = nasal. B. Characteristic visual cortex responses to each retinal stimulus. C. The location of the visual cortex response to each of the retinal stimuli is shown following applying a gaussian filter. D. Visual cortex retinotopic mapping in response to the eight retinal stimuli showing a clear organization. Each color represents the location of the response to the matched retinal stimuli. E. The center of activation of each of the responses (presented in diamond shapes with each color corresponding to a different location similarly to D) is shown in a larger magnification. A = anterior, L = lateral, P = posterior, M = medial.
Fig. 6. High-resolution retinotopic map with a non-responsive zone corresponding to a retinal lesion area. A. (Right) Retinal image of a 2 mm retinal area covered with laser lesions (white dots). (Left) Retinal image of the location of the eight stimuli, with the five most nasal ones positioned on healthy retina, whereas the three most temporal ones positioned on the lesioned retinal area (dashed white circle – demarcates the retinal lesion area). B. Diagram of the stimuli described in A. S = superior, T = temporal, I = inferior, N = nasal. C. Characteristic visual cortex responses to each stimulus, where the three most temporal ones showed no responses to stimuli positioned on the lesioned retina. D. The location of visual cortex responses to each of the retinal stimulus with no activity elicited in response to stimulation of the lesioned retina (dashed circle). E. Retinotopic mapping in the visual cortex showing no response in the presumed Lesion Projection Zone (LPZ). F. The centers of activations for each response (presented in diamond shapes with each color corresponding to a different location similarly to E) are shown in a higher magnification. A = anterior, L = lateral, P = posterior, M = medial.

response (Fig. 6(C) traces 3, 5, and 8, and in the corresponding cortical maps in Fig. 6(D)). Figure 6(E,F) present the combination of COAs that crossed the threshold, showing a clear retinotopic organization, whereas no responses were obtained from the damaged retina (dotted circle).
4. Discussion

We presented here a novel approach for image-controlled retinal stimulation to generate high-resolution VSD imaging of the visual cortex in rodents. Using a slit-lamp-based projection system, we obtained retinotopic mapping at an unprecedented resolution, down to a stimulus distance of 4.6 degrees in the visual field. The real-time camera-controlled stimulus system further enabled the stimuli to be localized to the desired retinal locations, enabling a comparison of cortical responses to normal and pathological retinal locations. Localized retinal stimuli with increasing irradiance elicited an increase in the response amplitude, reaching saturation at an irradiance of about 1000nW/mm², with the response latency remaining stable. These responses are similar to those reported by Pollack using VSDI [31] or to VEP responses in rodents [20,32]. The VSD imaging response to alternating grating decreased with increasing grating spatial frequency, similar to previous reports [33–35], reaching the noise level at about 16 cpm. The rats’ visual acuity is about 1-1.2cpd [34,36,37], which translates to a retinal resolution of around 17.4cpm, calculated for a nodal point distance of 3.3 mm [22], which is in agreement with our estimation. Previous work showed that the rat’s retinotopic structure translates nasal to temporal retinal stimuli into medial-posterior to lateral-anterior responses in V1 cortex [3,25,38,39]. Our results are consistent with this retinotopic organization for both the 4 and 8 grid stimuli (Fig. 4, 5, 6). More importantly, our high-resolution retinotopic mapping generated a resolution down to 4.6 degrees, significantly higher compared with previous reports in rodents. For example, a 20*20 deg retinotopy was reported in rats for both intrinsic signal imaging [25] and VSDI [3]. Similar to other reports, both of these studies used computer monitors or a back projection on a screen to present the visual stimuli at a distance of 30 cm from the rat eye. Previous reports showed that the rat’s eye refraction is usually highly ammetropic and hyperopic [40]. Thus, the use of the above-described set-up could reduce the obtained visual acuity or the electrophysiological signal [24]. The projection of the image onto the retina using our set-up, while controlling for the proper stimulus image quality by the retinal imaging system (Fig. 5(A)), enabled us to stimulate the retina at a higher image quality, and thus probably increased the response and enabled higher resolution mapping. Considering the high temporal resolution of the DMD, the system can be used at a higher stimulation rate which is limited by the functional temporal resolution of the dye-based imaging used for recording the cortical responses. The real-time control of the retinal stimulation location provided by our system has important advantages over the use of an ophthalmoscope back-projection, which is usually used in similar experiments [3] where eye movements or other causes of stimulus location shift cannot be properly controlled, nor can the accurate location of a stimulus to a specific retinal location. Using the controlled localized retinal stimulation provided by the retinal imaging system, we were able to demonstrate a small scotoma caused by a laser-induced retinal lesion of 2 mm. This capability is of great importance for studying various processes, such as the cortical reorganization caused by sensory deprivation, as reported previously [3,30]. Future adaptation of the system to include additional light wavelengths (e.g., near-IR or UV) can further enable studying of the cortical responses to localized retinal treatments, such as cellular therapy, optogenetics, or retinal prostheses [20,35].

5. Conclusion

We demonstrated here a high-resolution retinotopic mapping of the visual cortex in rodents, using a direct retinal projection system, which further enables the real-time control of retinal stimulus locations. This approach may prove to be an important investigative tool in the field of visual neuroscience.
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Disclosures
The authors declare that there are no conflicts of interest related to this article.

References
1. D. H. Hubel and T.N. Wiesel, “Receptive fields of single neurones in the cat’s striate cortex,” J. Physiol. 148(3), 574–591 (1959).
2. S. Chemla, A. Reynaud, M. di Volo, Y. Zerlaut, L. Perrinet, A. Destexhe, and F. Chavane, “Suppressive traveling waves shape representations of illusory motion in primary visual cortex of awake primate,” J. Neurosci. 39(22), 4282–4298 (2019).
3. G. Palagina, U. T. Eysel, and D. Jancke, “Strengthening of lateral activation in adult rat visual cortex after retinal lesions captured with voltage-sensitive dye imaging in vivo,” Proc. Natl. Acad. Sci. U. S. A. 106(21), 8743–8747 (2009).
4. D. Jancke, “Catching the voltage gradient—asymmetric boost of cortical spread generates motion signals across visual cortex: a brief review with special thanks to Amiram Grinvald,” Neurophotonics 4(3), 031206 (2017).
5. A. Grinvald and R. Hildesheim, “VSDI: a new era in functional imaging of cortical dynamics,” Nat. Rev. Neurosci. 5(11), 874–885 (2004).
6. S. Chemla and F. Chavane, “Voltage-sensitive dye imaging: Technique review and models,” J. Physiol. 104(1-2), 40–50 (2010).
7. V. Tsytsarev, L.-D. Liao, K. V. Kong, Y.-H. Liu, R. S. Erzurumlu, M. Olivo, and N. V. Thakor, “Recent Progress in Voltage-Sensitive Dye Imaging for Neuroscience,” J. Nanosci. Nanotechnol. 14(7), 4733–4744 (2014).
8. A. Grinvald, D. Shaham, A. Shmuel, D. Glaser, I. Vanzetta, E. Shroyer, H. Slovin, C. Wijnbergen, R. Hildesheim, and A. Arieli, “In-vivo Optical Imaging of Cortical Architecture and Dynamics,” Modern Techniques in Neuroscience Research 893–969 (1999).
9. A. Grinvald, R. D. Frostig, E. Lieke, and R. Hildesheim, “Optical imaging of neuronal activity,” Physiol. Rev. 68(4), 1285–1366 (1988).
10. Y. Chen, W. S. Geisler, and E. Seidemann, “Optimal decoding of correlated neural population responses in the primate visual cortex,” Nat. Neurosci. 9(11), 1412–1420 (2006).
11. H. Slovin, “Long-Term Voltage-Sensitive Dye Imaging Reveals Cortical Dynamics in Behaving Monkeys,” J. Neurophysiol. 86(6), 3421–3438 (2002).
12. E. Meirovithz, I. Ayzenstiat, Y. S. Bonneh, R. Itzhack, U. Werner-Reiss, and H. Slovin, “Population response to contextual influences in the primary visual cortex,” Cereb. Cortex 20(6), 1293–1304 (2010).
13. D. B. Omer, R. Hildesheim, and A. Grinvald, “Temporally-structured acquisition of multidimensional optical imaging data facilitates visualization of elusive cortical representations in the behaving monkey,” NeuroImage 82, 237–251 (2013).
14. D. Shoham, D. E. Glaser, A. Arieli, T. Kenet, C. Wijnbergen, Y. Toledo, R. Hildesheim, and A. Grinvald, “Imaging cortical dynamics at high spatial and temporal resolution with novel blue voltage-sensitive dyes,” Neuron 24(4), 791–802 (1999).
15. D. Sharon, D. Jancke, F. Chavane, S. Na’aman, and A. Grinvald, “Cortical response field dynamics in cat visual cortex,” Cereb. Cortex 17(12), 2866–2877 (2007).
16. M. T. Lippert, K. Takagaki, W. Xu, X. Huang, and J.-Y. Wu, “Methods for voltage-sensitive dye imaging of rat cortical activity with high signal-to-noise ratio,” J. Neurophysiol. 98(1), 502–512 (2007).
17. T. D. Mrsic-Flogel, S. B. Hofer, C. Creutzfeldt, I. Cloez-Tayarani, J. Changeux, T. Bonhoeffer, and M. Hübener, “Altered map of visual space in the superior colliculus of mice lacking early retinal waves,” J. Neurosci. 25(29), 6921–6928 (2005).
18. S. Schuetz, T. Bonhoeffer, and M. Hübener, “Mapping retinotopic structure in mouse visual cortex with optical imaging,” J. Neurosci. 22(15), 6549–6559 (2002).
19. E. M. Drakakis, N. Grossman, M. S. Grubb, R. B. Palmini, M. A. A. Neil, K. Nikolic, M. D. Dawson, B. McGovern, J. Burrone, P. Verho, Z. Gong, G. T. Kennedy, and P. Degenaar, “Multi-site optical excitation using ChR2 and micro-LED array,” J. Neural Eng. 7(1), 016004 (2010).
20. Y. Mandel, G. Goetz, D. Lavinsky, P. Huie, K. Mathieson, L. Wang, T. Kamins, L. Galambos, R. Manivanh, J. Harris, and D. Palanker, “Cortical responses elicited by photovoltaic subretinal prostheses exhibit similarities to visually evoked potentials,” Nat. Commun. 4(1), 1980 (2013).
21. S. Y. Shim, S. Gong, M. I. Rosenblatt, D. Palanker, A. Al-Qahtani, M. G. Sun, Q. Zhou, L. Kanu, F. Chau, and C. Q. Yu, “Feasibility of Intracocular Projection for Treatment of Intractable Corneal Opacity,” Cornea 38(4), 523–527 (2019).
22. A. Hughes, “A schematic eye for the rat,” Vision Res. 19(5), 569–588 (1979).
23. S. Remtulla and P. E. Hallett, “A schematic eye for the mouse, and comparisons with the rat,” Vision Res. 25(1), 21–31 (1985).
24. D. O. Mutti, J. N. Ver Hoeve, K. Zadnik, and C. J. Murphy, “The artifact of retinoscopy revisited: comparison of refractive error measured by retinoscopy and visual evoked potential in the rat,” Optom. Vis. Sci. 74(7), 483–488 (1997).
25. C. Gias, N. Hewson-Stoate, M. Jones, D. Johnston, J. E. Mayhew, and P. J. Coffey, “Retinotopy within rat primary visual cortex using optical imaging,” NeuroImage 24(1), 200–206 (2005).
26. P. Polack and D. Contreras, “Long-range parallel processing and local recurrent activity in the visual cortex of the mouse,” J. Neurosci. 32(32), 11120–11131 (2012).
27. H. Lorach, X. Lei, L. Galambos, T. Kamins, K. Mathieson, R. Dalal, P. Huie, J. Harris, and D. Palanker, “Interactions of Prosthetic and Natural Vision in Animals With Local Retinal Degeneration,” Invest. Ophthalm. Visual Sci. 56(12), 7444 (2015).
28. D. Birch and G. H. Jacobs, “Spatial contrast sensitivity in albino and pigmented rats,” Vision Res. 19(8), 933–937 (1979).
29. L. Multer, F. Chavane, J. Reynolds, and T. J. Sejnowski, “Cortical travelling waves: mechanisms and computational principles,” Nat. Rev. Neurosci. 19(5), 255–268 (2018).
30. H. Lorach, G. Goetz, R. Smith, X. Lei, Y. Mandel, T. Kamins, K. Mathieson, P. Huie, J. Harris, A. Sher, and D. Palanker, “Photovoltaic restoration of sight with high visual acuity,” Nat. Med. 21(5), 476–482 (2015).
31. P. Dean, “Visual pathways and acuity in hooded rats,” Behav. Brain Res. 3(2), 239–271 (1981).
32. G. T. Prusky, P. W. West, and R. M. Doulaous, “Behavioral assessment of visual acuity in mice and rats,” Vision Res. 40(16), 2201–2209 (2000).
33. F. Han, N. Caporale, and Y. Dan, “Reverberation of Recent Visual Experience in Spontaneous Cortical Waves,” Neuron 60(2), 321–327 (2008).
34. S. Roux, F. Matonti, F. Dupont, L. Hoffart, S. Takerkart, S. Picaud, P. Pham, and F. Chavane, “Probing the functional impact of sub-retinal prosthesis,” eLife 5, e12687 (2016).
35. M. T. Block, “A note on the refraction and image formation of the rat’s eye,” Vision Res. 9(6), 705–711 (1969).