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Catching the voltage gradient—asymmetric boost of cortical spread generates motion signals across visual cortex: a brief review with special thanks to Amiram Grinvald

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Abstract. Wide-field voltage imaging is unique in its capability to capture snapshots of activity—across the full gradient of average changes in membrane potentials from subthreshold to suprathreshold levels—of hundreds of thousands of superficial cortical neurons that are simultaneously active. Here, I highlight two examples where voltage-sensitive dye imaging (VSDI) was exploited to track gradual space-time changes of activity within milliseconds across several millimeters of cortex at submillimeter resolution: the line-motion condition, measured in Amiram Grinvald's Laboratory more than 10 years ago and—coming full circle running VSDI in my laboratory—another motion-inducing condition, in which two neighboring stimuli counterchange luminance simultaneously. In both examples, cortical spread is asymmetrically boosted, creating suprathreshold activity drawn out over primary visual cortex. These rapidly propagating waves may integrate brain signals that encode motion independent of direction-selective circuits. © The Authors. Published by SPIE under a Creative Commons Attribution 3.0 Unported License. Distribution or reproduction of this work in whole or in part requires full attribution of the original publication, including its DOI. [DOI: [10.1117/1.NPh.4.3.031206](https://doi.org/10.1117/1.NPh.4.3.031206)]

Keywords: voltage-sensitive dye imaging; V1 motion encoding; line-motion; luminance counterchange; cortical propagation.

Paper 16068SSVR received Nov. 18, 2016; accepted for publication Jan. 12, 2017; published online Feb. 10, 2017.

1 Introduction—Voltage-Sensitive Dye Imaging *In Vivo*, the Groundbreaking Step

The use of voltage-sensitive dye as a probe for optical detection of excitation across neuronal membranes started with experiments on nerve trunks from the legs of lobsters and spider crabs¹ and with recordings of single cell action potentials in neurons of leech segmental ganglia.² More than twenty years later, a further breakthrough for this technique was established when Grinvald et al.³ demonstrated voltage-sensitive fluorescent recordings from monkey primary visual cortex. This represented the first successful *in vivo* real-time imaging of activity within the mammalian cortex (but see Ref. 4). Using this technique, Grinvald and colleagues could, for the first time, visualize at the functional level how a small visual stimulus (a square of light) produces far-spreading activity in primary visual cortex (V1), much beyond the region of thalamic input (Fig. 1). Hence, the method provided direct evidence of the impact of dendritic integration and the functional properties of long-range horizontal connections^{5–8} at the neuronal population level.

Because from then on voltage-sensitive dye imaging (VSDI) was shown to allow for recordings along a continuum of membrane potentials, far spread interactions of neuronal populations across long-range connections, constituting gradual input from outside the classical receptive field,⁹ became optically accessible.

Moreover, in animals with small brains, such as mice, the wide field of view provided by high numerical aperture¹⁰ (several square millimeters of cortex), permitted simultaneous recordings of multiple brain areas.¹¹ Finally, the major advantage

of VSDI, that is, its high spatiotemporal resolution in capturing large-scale subthreshold activations, makes it possible to track widespread interactions within and across different cortical areas (including frontal regions) during sensorimotor tasks,^{12,13} giving experimental access to key theoretical questions related to cerebral coding strategies during behavior.^{14–16}

2 Catching the Voltage Gradient—Retinotopic Motion Signals Across V1

What would be a simple and straightforward stimulation paradigm to image the local propagation of subthreshold activity, and in particular, its functional impact on V1 output? To explore this question, Amiram Grinvald gave me the unique opportunity to measure cortical responses to the line-motion paradigm¹⁷ during my time as a postdoc in his laboratory (where Amos Arieli, Dahlia Sharon, David Omer, and Ivo Vanzetta introduced to me the demanding surgery and imaging procedures with invaluable patience). In the line-motion paradigm [Fig. 2(a)], illusory motion is perceived along a line flashed briefly after the presentation of a small spot, such that the line appears drawn out from the location of the preceding spot [Fig. 2(b)]. Hence, it was hypothesized that the sensation of motion evoked by the subsequently flashed line could result from sequential suprathreshold activation mimicking real motion drawing away from the local cue.^{17–20}

Figure 2(c) shows cortical responses (in V1 of an anesthetized cat) evoked by the spot when it was flashed alone.²⁰ Consistent with spreading along horizontal connections, postsynaptic subthreshold activity propagated at a speed of ~ 0.1 m/s (Refs. 3 and 9) and extended far beyond the suprathreshold retinotopic representation of the square (reddish colors encircled by

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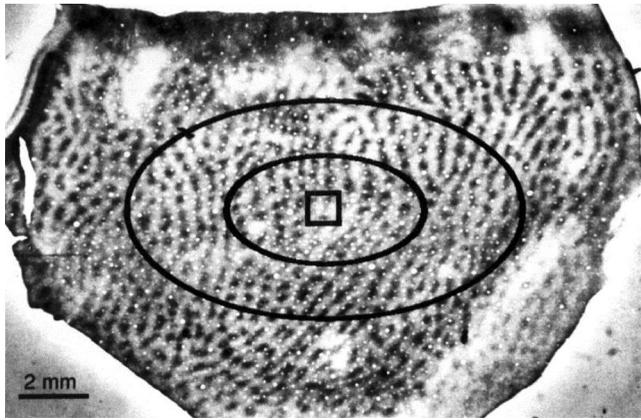


Fig. 1 Horizontal connections and the cortical point-spread function. Histological section of cortical tissue after staining with cytochrome oxidase that visualizes the regular mosaic pattern of oxidase blobs in V1 (Macaque monkey). The small square in the center of the image approximates the region that is activated by feedforward thalamic input using a visual stimulus as small as $0.5 \text{ deg} \times 0.25 \text{ deg}$ in size. The center ellipse delineates the region where activity measured with VSDI dropped to $1/e$ (37%); the outer ellipse refers to decline of $1/e^2$ (14%) of an approximated exponential fit to the data. What is exemplified here is that due to activity across long-range horizontal connections, a much larger region was covered than expected from direct thalamic input (square in the middle). As a consequence, $>10^7$ neurons are involved in the processing of even such a small and most simple square stimulus. Reproduced with permission from Ref. 3.

black contours). The second stationary stimulus, the bar that was flashed alone 60 ms later, yielded a similar finding [Fig. 2(d)]—that is, high-level activity delineated a circumscribed region representing the elongated retinotopic shape of the bar almost immediately (arrows). In contrast, when the line-motion condition was presented, we found that high-amplitude activity did not remain stable, but was gradually drawn out toward the end of the cortical bar representation [Fig. 2(e), lower arrows]. To compare how physical motion is represented across exactly the imaged cortical area, the small square was moved across the same region as that covered by the bar [Fig. 2(f)]. Similar to the line-motion condition, the moving square evoked high-amplitude activity propagating anteriorly (see black contours and lower arrows), reflecting the retinotopic motion trajectory of the square. In summary, using the line-motion paradigm, we were able to visualize directly how the horizontal cortical spread of activity was gradually boosted when a second stimulus appeared in rapid succession to the first. Hence, perception of apparent line-motion under our conditions¹⁹ may establish “seeing” one’s own previously subthreshold propagating activity that is gradually and asymmetrically boosted above detection threshold.

These observations suggest that higher brain areas may directly use retinotopic motion signals for creating the perception of motion. In support of this idea, we recently showed—using another paradigm that creates apparent motion perception in humans—how asymmetrically propagating activity resembles the perceived direction of motion.²¹ Once again, the high spatiotemporal resolution of VSDI enabled us to track activity

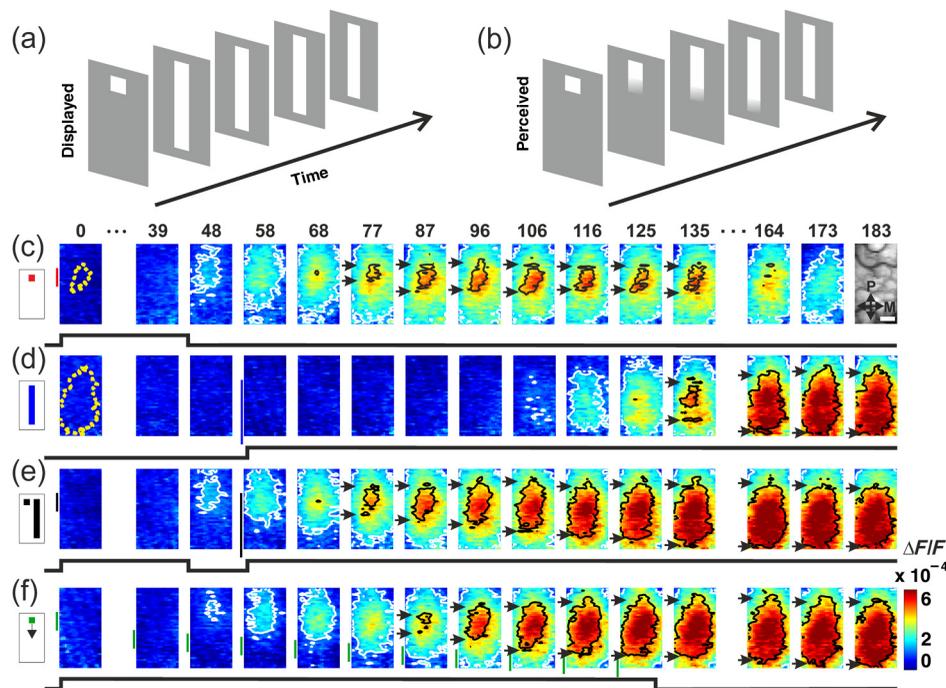


Fig. 2 Boosting of cortical spread in the line-motion paradigm. (a) The line-motion condition: A small spot (“cue”) is briefly presented before a bar stimulus. (b) Human subjects report illusory line-drawing. (c)–(f) VSDI of patterns of evoked cortical activity as a function of time (average across 22 repetitions). Yellow dotted contours approximate retinotopic representation of the stimuli. White contours delimit low-amplitude activity (significance level; $p < 0.05$). The cortical area imaged is shown at upper right. Scale bar 1 mm; P, posterior; M, medial. Green vertical lines in (f) indicate estimated position of the stimuli along posterior–anterior axis. Time in milliseconds after stimulus onset is shown at the top. Stimulation time is shown at the bottom of each row. Color scale indicates averaged fractional changes in fluorescence intensity ($\Delta F/F$). Stimuli: (c) flashed small square. (d) Flashed bar. (e) Line-motion paradigm. (f) Moving small square (32 deg/s). Modified from Ref. 20.

within milliseconds across several millimeters of cortex at sub-millimeter resolution (Fig. 3).

Specifically, we imaged cortical responses after two squares presented at neighboring locations counterchanged luminance at the same time²² (i.e., there was a luminance decrement for one square and a luminance increment for the other; see icons in Fig. 3). The first row in Fig. 3 depicts the case in which the upper square was darkened, whereas the neighboring lower square was brightened. Starting from the initial region of the cortical responses representing the upper square (posterior in the images), activity was successively drawn out toward the cortical location representing the brightened square (as indicated by the downward arrows). Thus, similar to the line-motion condition and as observed with squares moving continuously through visual space at high velocities [Figs. 2(e) and 2(f)], we found an asymmetric propagation of activity that was continuously elongated in the form of a cortical motion streak (for similar observations using subsequently flashed squares in an apparent motion paradigm, see Refs. 23 and 24). When the polarity of the luminance changes was reversed, the trajectory was also reversed (Fig. 3, bottom row). Thus, in both cases, a wavefront of activity propagated from the cortical sites representing the darkened stimulus toward locations representing the brightened stimulus. Because we found faster rise times (~ 10 ms) and faster decay for the bright to dark than the dark to bright changes, our results suggest that dark and bright spatiotemporal asymmetries^{25–33} provide a main driving force for this effect. Moreover, we proposed that the observed propagation may play a role in the generation of V1 motion signals that are independent of contrast polarity³⁴ (for review, see Ref. 35). In principle, any feature could create these activation

changes³⁶ (e.g., a contrast edge or a bright luminance patch moving from one retinal location [activation decreases] to another [activation increases]). This flexibility provides redundancy that is crucial for perceiving object motion in natural environments when some object features are hard to discriminate from their background. Such flexibility also allows features that contribute to perceiving an object's motion to become salient for the perception of the object's shape and the discrimination of the object from others in the scene.

Note that the asymmetric propagation occurred within a narrow range of signal amplitudes and could possibly be detected through the VSDI technique only at high signal-to-noise ratios and if the difference in activity between the locations representing the luminance counterchange was steep enough. This observation fits well with the recent discovery that luminance polarity is encoded by modular maps across V1.^{37–39} Consequently, the steepness of the gradient of activities produced between two cortical locations is critically dependent on where exactly the luminance counterchange occurs (e.g., dark input to a cortical patch that codes for light and vice versa will create only mild gradients). In fact, we speculate that the mechanism might either demand spatial integration over larger parts of a visual scene or that it is most effective at high-contrast stimulus borders where the luminance profile allows for overcoming noise associated with the detection of spatiotemporal gradients—as suggested in theoretical approaches to human motion detection.^{40,41}

To summarize, in both motion examples presented here, the main point in terms of the proposed underlying cortical mechanisms is that delayed input boosted subthreshold spread induced by preceding input. This created a gradual and asymmetrical propagation of mass population activity across

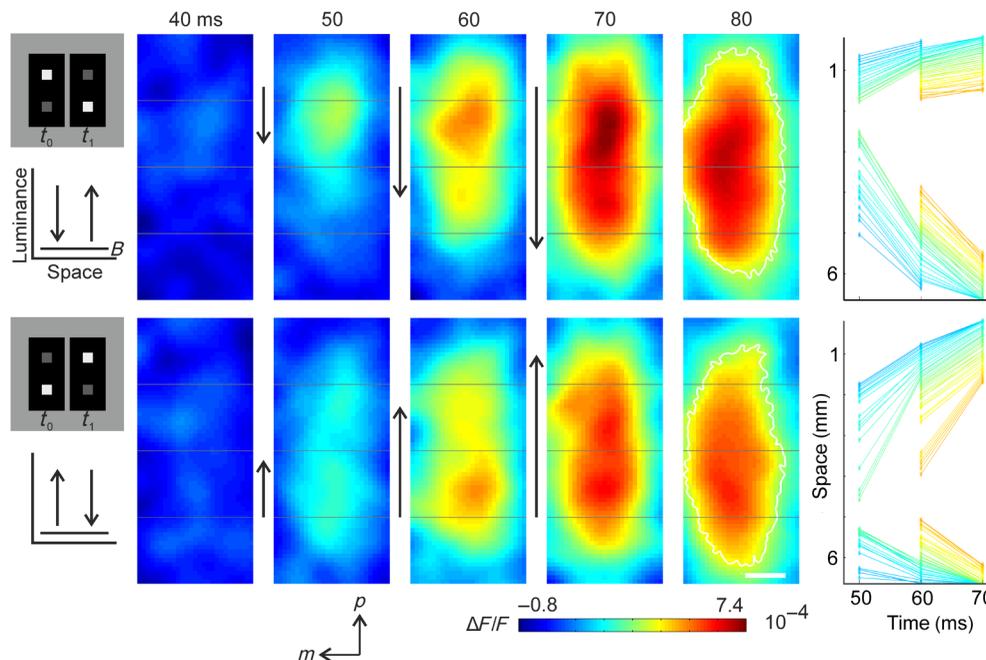


Fig. 3 Boosting of cortical spread through counterchange of luminance at two neighboring locations. First row: upper square turns dark, whereas lower square turns bright (B, background). Second row: lower square turns dark and upper square turns bright. Colorbar indicates activity levels (average across 24 repetitions). White contours in right frames encircle amplitude levels with Z -score > 3 . White bar in frame at bottom right = 1 mm, horizontal reference lines are 1.6 mm apart. Right column: space-time plots of activity in 1% steps (30% to 70%) of maximum amplitude. Line colors match color scale of image frames. Each line connects locations with same amplitude levels (mean across the central 7 pixels constituting each wave front and back) in anterior and posterior directions. Reproduced from Ref. 21.

retinotopic cortical coordinates, even though no physical (stimulus) motion was present. Interestingly, using a two-stroke apparent motion paradigm and intracellular recordings, facilitation of previously initiated subthreshold spread was demonstrated to be most effective when the stimulus onset asynchrony was as short as 20 milliseconds.^{42,43} In the case of the line-motion condition, the required asynchrony may be provided by the visual stimulation itself (first the flash, then the bar), whereas in the case of the luminance counterchange condition (synchronous by definition), asynchrony emerges from the intrinsic temporal offset between the processing of stimulus darkening and brightening. Clearly, in both conditions additional suppressive normalization mechanisms are most likely involved,^{44–48} as significant subadditivity was shown for both examples.^{20,21}

3 Where is Propagation in V1 Decoded and When?

The claim that local motion signals in V1 are encoded in terms of retinotopically and asymmetrically propagating activity may appear trivial at first sight. In light of the well-known retinotopic organization of V1,^{49–51} any shift of a stimulus across receptive fields must lead to propagation of activity at the population level, both in stimulus space⁵² and in cortical coordinates. For instance, using VSDI to record cortical responses to standard drifting gratings, we visualized (for the first time though) the expected retinotopic propagation of the gratings' stripes across simultaneously active orientation domains.³¹ In addition, and surprisingly, we also found a salient propagation of the gratings' first harmonics, possibly indicating increased strength of V1 responses for dark versus light stimuli.^{32,53} Note that such retinotopic waves could be used by higher cortical areas to resolve ambiguities that are inherent to maps formed by solely spatiotemporal filtering of moving stimuli.^{54,55} More importantly, however, in all cases shown here subthreshold activity spread ahead of thalamic input, enabling cortical neurons to "sense" regions beyond their classical receptive field borders.⁵⁶ Thus, stimuli moving coherently in visual space generate a wave that activates cortical locations in front of the stimulus's trajectory [Fig. 2(f)]. This property may become particularly relevant when an object moves quickly, as neuronal processing delays may create the problem of being perceptually offset from their physical position.^{57,58} Subthreshold spread may, therefore, constitute a possible substrate for preactivation, as has been additionally implied by psychophysical studies in humans.⁵⁹ As a consequence, cortical processing times may partially be compensated by preactivation to allow for faster spiking for a moving stimulus as compared to a single flash.^{20,52,60} Such an anticipatory mechanism implies immediate processing which is eventually coupled to immediate awareness (but see Ref. 61).

In any case, both examples highlight a second important signature of retinotopic motion signals propagating in V1. That is, following the propagating wavefront, a motion streak was generated. Using a population approach, it has been shown earlier that such cortical streaks contain information about the orientation of an object's trajectory.⁶² In other words, a second stimulus feature (here orientation) that was not present instantaneously (and not in the physical stimulus) was formed sequentially through spatiotemporal integration of the motion path. On the one hand, the emergence of motion streaks appears undesirable for sensation and indeed, mechanisms exist to suppress them.^{60,63–65} In contrast, it has been shown that information

about motion axes is still present across neuronal activity and can be extracted from motion streaks.^{66–70} Thus, motion streaks may be analyzed unconsciously and separately over time^{71–74} to contribute to further analysis such as form-from-motion at higher processing stages.^{20,21,62,69,70,75–80}

Interactions mediated by propagating waves of cortical population activity across V1 have been demonstrated for a variety of mammalian species (for example, see Refs. 20 and 81–91). Functional implications of these waves have been discussed in different contexts such as plasticity,^{92,93} contrast normalization,^{94,95} and feedback from higher brain areas due to apparent motion stimuli.^{24,96,97} There is no clear answer to where and when these signals are finally integrated to form perception. However, regardless of whether the propagating activity as reported here may directly subserve "perceptual knowledge" or initially "hidden" cortical analysis of motion,⁷¹ any retinotopic encoding of motion further downstream through propagating waves must engage mechanisms that emerge from the topography of early cortical areas such as V1.^{69,98} Indeed, characterizing human motion detectors in space-time coordinates⁹⁹ led to the discovery of a previously unknown brief increase in detector amplitude at motion onset.¹⁰⁰ The perceptual relevance of retinotopic encoding of motion trajectories in V1 (Ref. 101) was, furthermore, demonstrated using a "path-guided" apparent motion paradigm in combination with fMRI.¹⁰² The above authors found a curved illusory filling-in of the motion path in V1 that strongly correlated with the observers' perception.¹⁰² Strikingly, in behaving mice, activity trajectories in V1 correlated with bistable perceptual switches using an apparent motion quartet as a stimulus.⁹⁷ Altogether these results imply that retinotopically propagating activity across V1, as observed in the presented studies, may have implications for the encoding of signatures of motion and may influence perceived shape dependent on the dynamics of the read-out at higher brain stages.

4 Importing VSDI Techniques from Israel to My Lab in Germany

It is noteworthy to emphasize that Amiram Grinvald's support and help was most valuable for the adventure of building up an imaging system in my own laboratory, where we used VSDI in a variety of settings. For example, we were the first using VSDI to record V1 population activity patterns in response to natural movies,¹⁰³ revealing increased sparseness,^{104,105} a larger fraction of space-time inseparable dynamics,¹⁰⁶ and a more effective balance between excitation and inhibition^{107,108} in comparison to simple grating stimuli.¹⁰³ Using VSDI, we showed predictive coding in V1 in a strict sense, signifying differences in feature representation (i.e., orientation) of past and present inputs.¹⁰⁹ We also pioneered the use of VSDI in pigeons¹¹⁰ and showed that these highly visual animals have no orientation maps in the assumed homolog of mammalian V1. Instead, we demonstrated overrepresentation of vertical orientation, possibly as a result of adaptation to biased input statistics.^{35,111} Furthermore, we used VSD to image for the first time the trigeminal ganglion of rats, showing the formation of activity pattern in response to various volatile substances.¹¹² Recently, we used VSDI to explore the effects of transcranial magnetic stimulation (TMS) on V1 activity and its induced plastic changes.¹¹³ In these settings (i.e., using light as a measure), VSDI has the advantage of being able to avoid interference with the strong TMS-induced electric field.

5 Conclusions

VSDI enables to record neuronal ensemble activity over a wide field of view with high precision. Hence, evoked space-time interdependencies between large pools of cortical neurons can be measured with high spatiotemporal accuracy, as exemplified here. Also information encoded by synchrony¹¹⁴ or decorrelation mechanisms¹¹⁵ within spatiotemporal activity patterns^{116,117} can be obtained, which may otherwise be detected using only densely spaced multielectrode arrays. Likewise, any systematic mapping (if orthogonal to the image plane) of visual stimulus parameter combinations that are represented across groups of neurons can be tracked instantaneously across cortical coordinates,³¹ as the optically measured activity provides an immediate link to the functional cortical architecture.^{118–120} Here, two examples in the visual domain were presented, where propagation of cortical activity emerges from local space-time imbalances in the computation of external input.^{20,21} The crucial factor for both instances is that local input creates cortical spread, which builds up a gradient of activity—from sub-threshold to suprathreshold levels. The initial temporal advance in the generation of precuing activity enables subsequent input to boost asymmetric propagation of suprathreshold activity in V1. The following emergence of cortical motion streaks indicates additional integration processes over time.^{42,43,62,67,69,103}

However, there are some disadvantages of the method worthy of discussion. From a purely technical point of view, besides being restricted to surface cortical regions, the method does not permit the use of freely moving subjects. Thus, head-fixed preparations must be applied, at least at the time of this writing. From a physiological viewpoint, although some recently reported interaction with GABAA receptors¹²¹ might be of negligible size,^{122,123} it remains largely unexplored how far pharmacological side effects might possibly affect the signal.¹²⁰ In addition, the often found relatively low signal-to-noise ratio (significantly influenced by “biological noise”) frequently requires averaging across repeated trials. However, it should be noted that advanced postprocessing algorithms^{31,90,124,125} and excellent handling of the method allows single-trial read-outs in anaesthetized, awake, and also in the behaving animal (for example, see Refs. 84, 90, 115, and 116). The fact that the portion of activity originating from distinct (e.g., inhibitory or excitatory) populations of neurons cannot be distinguished is a disadvantage for addressing questions related to interactions between different cell-specific circuitries (note that, on the upside, it avoids biased sampling of neurons and captures net population activity irrespective of preferred feature selectivity, thus providing an accurate picture of the global state of the cortex). Moreover, the wide spread of activity observed with VSDI (up to several millimeters) might include contributions from fibers of passage that shadow spatiotemporal interactions between more closely coupled groups of neurons. Finally, the use of voltage-sensitive dyes requires craniotomy in animal models and in most cases also removal of the dura to obtain proper staining. The staining itself may occupy potential measurement times. Most important, however, is that the invasive nature of the procedure hinders chronic monitoring as it bears the risk of tissue irritation or invoking inflammatory processes. Recently developed genetically encoded voltage indicators (GEVIs) may improve upon such technical shortcomings related to VSDI.¹²⁶ In particular, GEVIs allow targeting of specific cell populations and, thus, provide the unique property of selective staining of specific cell types. We may await even more exciting times once

these methodologies are available in species other than the current dominant mouse model.

“For every change, you pay” was a favorite sentence that I heard from Amiram Grinvald whenever I enthusiastically suggested new settings or experimental approaches during my postdoc time in his lab. He certainly knew better than me after having laid the foundation of *in vivo* wide-field optical imaging of voltage changes across cerebral cortex.

Disclosures

The author declares no conflicts of interest.

Acknowledgments

The author was funded by Minerva Fellowship (The German Federal Ministry for Education and Research) and by grants from the Deutsche Forschungsgemeinschaft, SFB-874 (TP A2), German-Israeli Project Cooperation (DIP, JA 945/3-1, SL 185/1-1), SPP 1665 (JA 945/4-1), and the Bundesministerium für Bildung und Forschung, BMBF, Bernstein Group Computational Neuroscience Bochum.

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