Supplementary information S1 (box) | Comparing measurements from different modalities

Relating brain measurements across length scales from behavior and neuroimaging to spikes and sub-cellular changes is an important goal. It difficult, however, to demonstrate rigorously that measurements across scales and methods reflect the same phenomena. In the following sections we consider several putative connections between observations at different scales and methods.

A. Comparing electrophysiology and fMRI measures

A recent review of the literature groups a functional MRI study with an array of single-unit physiology reports:

“Topographically, V1 becomes remapped, with a shrinkage in the representation of the lesioned part of the retina and an expansion in the representation of the parts of the retina surrounding the lesion (Gilbert et al. 1990; Chino et al. 1992; Gilbert & Wiesel, 1992; Heinen & Skavenski, 1992; Eysel et al. 1999; Calford et al. 2000; Baker et al. 2005; Giannikopoulos & Eysel, 2006).”

One can find a similar grouping of references in an fMRI study:

“Extensive topographic reorganization of primary visual cortex (V1) has also been reported in adult cats and monkeys following discrete retinal lesions (Chino, Kaas, Smith, Langston, & Cheng, 1992; Chino, Smith, Kaas, Sasaki, & Cheng, 1995; Gilbert & Wiesel, 1992; Heinen & Skavenski, 1991; Kaas et al., 1990). Neurons in the deprived region of V1 (i.e., the region that previously responded only to stimuli falling on the subsequently lesioned part of the retina) became responsive to stimuli falling on parts of the retina adjacent to the lesioned area. … Here, we used fMRI to test for reorganization of visual processing in five individuals with extensive retinal damage from MD with different etiologies and ages of onset.”

The electrophysiological and fMRI measures data are dissimilar in important ways. Perhaps the most glaring is that the electrophysiological reports claim that deafferented cortex responds to stimuli that normally evoke responses in adjacent cortex. The neuroimaging data claim that cortex several centimeters away from preserved cortex is recruited.

To see the difference, consider the images in Figure S1. These images represent fMRI data reported in four macular degeneration subjects. Each has a scotoma spanning more than 10 deg in the central visual field. The authors identify all four subjects as supporting large-scale reorganization in V1. The response from intact retina is labeled as PRL (white arrow). Because of the macular degeneration, these authors believe that these subjects would not ordinarily have a foveal V1 response (but see REF). Hence, data demonstrating reorganization is based on the responses present in the portion of V1 that typically responds to foveal stimulation (white...
elliptical ROI). In the first study, the authors write “for both subjects (Fig. 2), visual stimulation, compared with the blank screen baseline, strongly activated the foveal confluence and adjacent cortical regions corresponding to the projection zone of the damaged retina.” On the other hand, “The activation of the foveal confluence and adjacent cortex by peripheral stimuli was not observed in matched control subjects.”

Figure S1. Responses in the visual cortex of subjects with macular degeneration. The images are flattened representations near calcarine cortex (V1). To create the flattened images, a cut is made along the calcarine sulcus so that the dorsal and ventral portions of V1 fall along the left margin (black dashed line, upper left image). The foveal representation is near the middle-left of the image (white outline); peripheral representations are in anterior calcarine, both above and below the middle-left (white arrows). Warm colors indicate a positive BOLD response; cool colors a negative response. Subjects MD1-A and MD2 were reported in REF2; subjects MD3 and MD5 were reported in REF3. The authors present these examples as supporting adult V1 plasticity (see text). PRL: preferred retinal locus, bottom arrows indicate activity expected based on the location of the stimulus in the periphery. White outline indicates the foveal confluence. White scale bar: ~1 cm.

In three of the subjects the fMRI responses in regions normally corresponding to the PRL (white arrows) are separated by several centimeters from the putatively recruited responses in the foveal representations within the LPZ (white ellipses). This
contrasts with electrophysiology measurements; in that case cortical activation spreads at most a few millimeters from adjacent cortex into the LPZ. In addition to the very large difference in scale, there is a large silent zone in V1 separating between responsive cortex of the PRL and the putative reorganized activity. This type of reorganization, a response several centimeters away from the intact response, has not been described with conventional electrophysiological methods. Additional evidence should be provided before we accept that these two measurements reflect a common phenomenon.

One fMRI data set (MD1-A) is more consistent with the electrophysiological measures. In this subject the spatial scale of fMRI response is much larger than the electrophysiological spread, but there is no silent zone: the response extends continuously from the PRL to the foveal representation. Data from this subject have been reported in the literature using very similar methods on two occasions, and we show the second set of measurements in Figure S2. These differ from the first in that there is a large silent zone separating the PRL responses from the foveal responses, similar to the data from MD2, MD3 and MD5. Hence, further measurements should be undertaken to demonstrate whether or not this subject has a large silent zone.

In summary, much work remains to show whether or not the neuroimaging responses in these studies measure the same phenomenon as the electrophysiological studies. The current weight of the evidence is that they do not.

Figure S2. A second set of measurements in subject MD1. Methods and stimuli are very similar to the original report\(^2\). In the two data sets shown here the peripheral stimuli were presented at different locations and produced slightly different responses (white arrows). In both cases there is a response in foveal V1. In these measurements there is a large silent zone in V1 separating the peripheral (PRL) and foveal responses, in contrast to MD1-A where the activity appears to be confluent for several centimeters. The large intra-subject variability of statistical maps in this subject underscores the need of performing additional measurements in order to understand this phenomenon. Data from REF\(^5\), Figure 2.
B. Behavioral assays and V1 plasticity

Just as it is difficult to confidently connect neural measurements spanning length scales, it is also challenging to couple neural and behavioral measures. The peripheral pathways and in particular sensory encoding offer the best target for establishing a relationship between behavior and the nervous system. Connections between cortical signals and behavior are challenging to establish across all fields of neuroscience, though there have been some important achievements.

One recent report suggests a connection between V1 adult cortical plasticity and a visual shape illusion. Specifically, the shape illusion arises from patching one eye and presenting stimuli near the blind spot in the fellow eye. The illusion can be measured within seconds of applying the patch and disappears within seconds of removing the patch. This report is similar to illusions that have been observed near an artificial scotoma, rather than the natural scotoma of the blind spot. It is proposed that these rapid and reversible visual illusions are explained by the “rapid receptive field expansion within the deprived V1 as reported in electrophysiological studies after retinal lesions.” As we describe in the main text, there is an unsettled controversy about the effects of an artificial scotoma on V1 receptive fields. Moreover, this type of rapid and reversible phenomenon is generally in the category of sensory adaptation rather than adult cortical plasticity. Even so, it is possible that there could be a connection. How might it be demonstrated?

The most secure methods of demonstrating links between specific neural activity and a behavioral measure use independent quantification of the neural signals and behavior; these measurements are then coupled by a specific model defining how the measures are connected. The classic work on color-matching, in which quantification of the behavior and neural signals come together in perfect agreement is the best example.

The quantitative measurements comparing these shape illusions with adult V1 cortical plasticity do not agree well. For example, one study made measurements of filling-in using subjects with macular degeneration. These authors quantified the extent of the filling-in phenomenon and found that it was too large to be explained by measured plasticity in V1 circuitry. Another study found that the dependence of their effect on eccentricity was inconsistent with the V1 cortical magnification function, although they were reluctant to abandon the hypothesis that V1 mechanisms explained the phenomenon.

Related to the shape measurements, there have also been attempts to directly combine measurements of filling-in and plasticity. The Komatsu lab carried out a thorough set of studies examining perceptual filling-in responses to artificial and retinal scotomas. They found that “the normal visual system possesses a mechanism that yields filling-in when some part of the retina is damaged, and that such a mechanism requires no topographical reorganization in V1.” In the main text we noted other electrophysiological measures of filling-in that failed to support a connection between V1 signals and perceptual filling-in.

The quantitative measures in these experiments do not support a close coupling between the perceptual phenomena of filling-in, shape perception, and adult V1 plasticity. There are quantitative inconsistencies between the data, and there are no compelling models to explain how shape or filling-in could be predicted from the neural responses. To advance this field of inquiry, one must first achieve greater clarity about the neural measurements – the timing, size of the receptive field...
changes, and dependency on visual eccentricity. Once the neural measures are secure, we require a model that explains how receptive field size changes predict the visual shape illusion. Quantitative measurements that compare these perceptual and neural measures could then be used to prove—or disprove—the case.

C. Optical imaging

Optical imaging combined with electrophysiological measurements can promote a deeper understanding of the relationship between fMRI data and single unit data. The contrast signal measured by optical imaging is based on the same contrast mechanism as fMRI (blood oxygenation). Because optical imaging is generally invasive, it is possible to make electrophysiological measurements at the imaged cortical locations. Coordinating blood oxygenation and electrophysiological measurements from the same cortical region provides valuable information about the relationship between the two types of data.

Some readers of the main text were no doubt alarmed that we failed to cite an influential paper seeking to do just this in the area of adult cortical reorganization\textsuperscript{20}. That paper measured optical imaging and spiking responses in cat cortex and demonstrated that a small ($\sim$0.5 degree) stimulus evokes (a) spiking activity across a range of cortex (0.4-1.1mm) and, (b) subthreshold activity over a region extending $\sim$3-5 mm (for similar estimates in primate see REF\textsuperscript{21}). The authors then lesioned the retina and concluded that the extent of the subthreshold signal is linked to the degree of cortical reorganization: “In the reorganized cortex the spike PS expanded, approximating the extent of the optical PS seen in normal cortex (abstract)”.

The key optical images assessing reorganization are reproduced in Figure S3. The three images show orientation-preference estimates in a region of V1. A white line, indicating the upper edge of the estimated cortical scotoma, is shown on all the images. The limits of the scotoma were verified by electrode recordings. The three images (starting at the left) were measured before the binocular lesion, immediately after the lesion, and five months after the lesion. The authors write that “In the 'recovered' cortex, visually driven activity had returned, with the RFs shifted to positions outside the retinal lesion (REF\textsuperscript{20}, Caption of Figure 4).” The differences between pre-lesion and recovered orientation-preference estimates are shown in the fourth image. The authors conclude that orientation columns measured in deafferented V1 cortex form in the weeks following the retinal lesion and the recovered orientation-preferences “stayed roughly unchanged from the pre-lesion state, despite reorganization of RF input.”

Notice that immediately post lesion the signals are highly degraded in both deafferented cortex and control cortex. The reported restoration of orientation column structure in deafferented cortex is commensurate to that seen during the same time in control cortex. Hence, the optical imaging data do not show that deafferented cortex was more influenced by the binocular lesion than control cortex (which should have remained unchanged).
Figure S3. Images representing reorganization measured by optical imaging.
The three images on the left are orientation-preference estimates prior to lesion,
immediately following binocular lesions, and five months after recovery. The white
line separates nominally spared cortex (above) – which is intended to serve as a
control – from the lesion projection zone (below). Control cortex shows a marked
change in response immediately post-lesion compared to “Pre Lesion” and
“Recovered”. The responses in control cortex and the lesion projection zone evolve
together, making it difficult to argue convincingly that the changes inside the LPZ
differ from control cortex. Oriented lines at the bottom indicate the association
between color and preferred stimulus orientation. Images are from REF20, Figure 4.

It is possible the authors are correct; but the data in this brief study need to be
made more convincing. Among the issues one might consider in designing a more
complete optical imaging study are these: How faithfully does the optical image
signal reflect subthreshold activity? Can we compare the signal amplitude between
deaferented and control cortex? Can we measure the retinal recovery in the
penumbra of the lesions and compare this with the changes at the border of the LPZ?
Can we use quantitative methods to measure the receptive field properties in the LPZ
and control cortex? Can we interpret the relationship between the two data sets using
a model that relates the properties of the single-unit recordings and the optical image
data, accounting for sampling bias and cell diversity?

D. Synaptic and molecular dynamics
There is a substantial literature analyzing stability and plasticity of synaptic processes
in adult V122-30. The experimental methods for synaptic measurements are evolving at
a rapid pace, but there can be little doubt that in several cases there are activity-
dependent changes at the scale of the dendritic and axonal arbors. The implication of
these synaptic level changes for receptive field properties – or, even more
importantly, for visual behavior – should be investigated. Further, there are important
open questions about the influence of the invasive experimental methods themselves,
which can involve skull removal and penetration of the dura31. This literature is well
beyond the scope of our review, but it is a good example of an important field where there are opportunities to explore the relationship across length scales and methods.

References

19. De Weerd, P., Gattass, R., Desimone, R. & Ungerleider, L.G. Responses of cells in monkey visual cortex during perceptual filling-in of an artificial...


