

## Journal Club

**Editor's Note:** These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see [http://www.jneurosci.org/misc/ifa\\_features.shtml](http://www.jneurosci.org/misc/ifa_features.shtml).

## Do Visual Circuits Mature Without Visual Stimuli?

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Review of Ko et al.

The mammalian neocortex is intricately and nonrandomly wired. Sophisticated neocortical circuits are essential for the emergence of complex brain functions. Recently, independent groups have asked whether the converse is also true; that is, does the function of cortical neurons drive their connectivity? (Ko et al., 2011; Ishikawa et al., 2014) The most direct observation of the interaction between circuit function and wiring comes from a series of papers by Ko and colleagues (Ko et al., 2011, 2013, 2014). In the first paper (Ko et al., 2011), it was established that neighboring neurons in layer II/III of mouse primary visual cortex are more likely to be connected to one another if they preferentially respond to similar visual stimuli. In a follow-up study (Ko et al., 2013), this feature-specific connectivity was shown to develop after eye opening [around postnatal day 14 (P14) in mouse]. The latest paper, recently published in *The Journal of Neuroscience* (Ko et al., 2014), introduces an intriguing finding: despite this connectivity being stimulus-specific and developing in the presence of visual function, it emerges independently of external visual inputs.

How can circuits defined by a common visual feature emerge if this defining feature plays no role in setting them up? We

divide our discussion into three parts. First, we review the evidence presented by Ko et al. (2014) and compare the development of these local microcircuits to other circuits of the visual system. Second, we discuss possible mechanisms by which feature-specific connections could emerge in the absence of visual experience. Third, we discuss what role visual experience might play in this.

The now well established technique used by Ko et al. first involves *in vivo* characterization of individual neuronal response profiles. This was achieved by two-photon population calcium imaging while presenting various visual stimuli to anesthetized mice. Then, the same brain was acutely sliced and up to six simultaneous whole-cell recordings were performed in acute coronal sections. Thus, the authors could test the synaptic connectivity of the same neurons whose sensory-evoked activities have been determined *in vivo* (Ko et al., 2011, 2013). Next, the authors performed the same response profiling and connectivity mapping in mice reared in darkness (i.e., deprived of visually evoked activity) from shortly before eye opening until the day of the experiment (P22–P26) and compared these results to those previously published. They found that the emergence of these feature-specific microcircuits generally did not require visual experience, but there were some interesting exceptions (Ko et al., 2014) (Fig. 1).

How does this compare to the development of other circuits in the visual system? The retinal circuitry develops before eye opening (Wong, 1999; Sanes and Yamagata,

2009). The same is true for retinogeniculate connections and downstream thalamocortical projections (Stellwagen and Shatz, 2002). Indeed, this feedforward system allows cortical neurons to be visually responsive with distinct receptive fields at eye opening (Ko et al., 2013). The development of these circuits does not depend on visual experience (Wong, 1999; Stellwagen and Shatz, 2002; Sanes and Yamagata, 2009). Conversely, local cortical connections form and are refined after eye opening (Ko et al., 2013; Ishikawa et al., 2014). For example, another paper recently published in *The Journal of Neuroscience* (Ishikawa et al., 2014) shows that nonrandom connectivity between layer IV and layer II/III pyramidal neurons develops following eye opening and is partially impaired by dark rearing. A similar time course and effect of dark rearing were observed for inhibitory interneurons (Moraes et al., 2002). The feature-selective connectivity uncovered by Ko and colleagues (2014) therefore shares features with both types of circuits: it develops independently of visual experience, but with a time course and activity-dependent refinement similar to those of other local cortical circuits.

The emergence of feature-selective connectivity provides a good model for understanding the formation of functional microcircuits. Interestingly, the most obvious mechanism (visual sensory experience) does not explain it. What else might? Spontaneous, spatiotemporally correlated waves of activity originating in the retina before eye opening are essential

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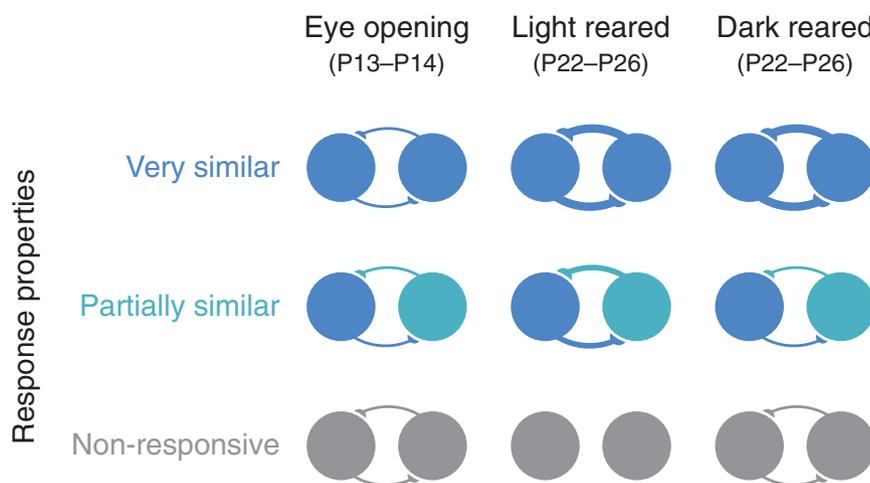
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for the accurate refinement of retinotectal projections (Stellwagen and Shatz, 2002). Ko et al. (2014) suggest that this may also apply to feature-selective cortical connectivity in dark-reared mice. This is unlikely to be a default mechanism when visual experience is available, since in these conditions, retinal waves rapidly degrade following eye opening (Sanes and Yamagata, 2009; Maccione et al., 2014). Alternatively, a different kind of spontaneous activity might explain the emergence of feature-selective connectivity. For example, the restricted spatial scale of the microcircuits studied by Ko et al. (connected cells are separated by  $<50 \mu\text{m}$ ) makes it plausible that they share, directly or indirectly, common inputs from other cells. Correlated activity in small groups of converging, tuned cells (retinal, thalamic, layer IV, or even layer II/III) could therefore be sufficient to drive the formation of these circuits. If input from single cells is strong enough to drive action potentials in layer II/III cells during development, the emergence of feature-selective microcircuits could be explained even in the absence of large-scale correlated activity.

Another possible explanation for the development of feature-selective connectivity without visual experience involves the common ontogenetic origin of neurons. A series of papers, mainly by Song-Hai Shi and colleagues, has convincingly shown that neurons from the same progenitor tend to be interconnected and share similar responses to visual stimuli (Yu et al., 2009; Li et al., 2012). Although this evidence is compelling, it is important to remember that ontogenetic clones only contain tens of cells, which cannot account for the thousands of inputs each cortical neuron receives. However, it is conceivable that a broader genetic program determines connectivity. Under this hypothesis, layer II/III neurons with similar stimulus responses would belong to a particular genetic class, expressing the same palette of adhesion molecules, which mediate axon–target recognition during development. This would echo what has been observed for synapses in the retina and for retinotectal projections (Sanes and Yamagata, 2009; Osterhout et al., 2011). The observations by Shi and colleagues could be entirely consistent with this hypothesis, since it is easy to imagine how neurons from the same progenitor share the same genetic program.

Whatever mechanism ultimately explains the emergence of functional con-



**Figure 1.** Schematic overview of findings by Ko et al. (2014). Cells that respond very similarly to visual stimuli generally increase connections after eye opening. This increase was also observed in the absence of visual experience. Cells that respond only partially similarly to visual stimuli show only a moderate increase in connectivity after eye opening, and this does not occur without visual experience. Visually non-responsive cells usually disconnect from other nonresponsive cells, but without visual experience these connections are maintained.

nectivity, it will do so in cooperation with visual experience. Ko et al. (2014) show that while cells sharing the exact same stimulus preference connect to one another in the absence of normal visual experience, remarkably, cells with only partially overlapping response profiles do not show the normal increase in connectivity when dark-reared. Similarly, cells that do not respond to visual stimuli usually disconnect from other nonresponsive cells, but this does not occur when dark-reared. This suggests more intricate refinement requires visual experience. Similar results have been obtained for other cortical circuits: the recent paper by Ishikawa et al. (2014) concludes that refinement of a subtly different microcircuit requires visual input.

Together, these results raise an important question: if refined functional connectivity is impaired by lack of visual experience, is the corresponding function also impaired? A key paper details the development of behaviorally relevant visual acuity (Kang et al., 2013). The authors show that complete visual acuity is rapidly reached in sighted mice  $\sim 2$  weeks after eye opening. Surprisingly, in dark-reared mice, visual acuity also develops, albeit at a slower rate, eventually reaching normal levels by 4 weeks after eye opening. When dark-reared mice are suddenly introduced to visual experience, the rate of acuity development greatly increases. A closer look at the results by Ishikawa et al. (2014) suggests that dark-reared circuits are on the way to maturation but proceeding at a slower than normal pace. This is particu-

larly evident when comparing the response amplitudes between connected layer II/III pairs, where dark-reared responses seem to be at a point between immature and mature. To test whether feature-selective wiring is also delayed (rather than impaired) by lack of visual experience, Ko et al. could prolong dark rearing and perform the same challenging experiments at later time points. Ultimately, it would be interesting to correlate the development of feature-selective circuits to a behavioral output (with and without dark rearing).

In all, the interaction between visual experience and circuit wiring could be summarized, as Ko et al. do, as a “balanced restructuring”. Evidence for a direct balancing between visual experience and a hard-wired intrinsic program is lacking thus far, but the concept captures nicely how different mechanisms may work in parallel to ultimately shape the connectivity, or function, of cortical circuits.

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