

Traveling Waves in Visual Cortex

Tatsuo K. Sato,¹ Ian Nauhaus,² and Matteo Carandini^{1,*}

¹University College London, London EC1V 9EL, UK

²Salk Institute, La Jolla, CA 92037, USA

*Correspondence: matteo@carandinilab.net

<http://dx.doi.org/10.1016/j.neuron.2012.06.029>

Electrode recordings and imaging studies have revealed that localized visual stimuli elicit waves of activity that travel across primary visual cortex. Traveling waves are present also during spontaneous activity, but they can be greatly reduced by widespread and intensive visual stimulation. In this Review, we summarize the evidence in favor of these traveling waves. We suggest that their substrate may lie in long-range horizontal connections and that their functional role may involve the integration of information over large regions of space.

Introduction

When Hubel and Wiesel published their first landmark papers on the primary visual cortex of the cat, they revealed that its neurons are exquisitely selective for stimulus attributes and that this selectivity defines orderly maps of functional architecture (Hubel and Wiesel, 1959, 1962). These discoveries echoed those made a few years earlier in somatosensory cortex (Mountcastle, 1957) and cemented a view of sensory cortex in which sharply tuned neurons arranged in vertical columns signal substantially different attributes from their neighbors displaced along the horizontal dimension. This view has been extremely fruitful in the subsequent 50 years and was further supported by advances in two-photon imaging. These revealed that maps of functional architecture are organized with crystalline precision down to the resolution of single cells (Ohki et al., 2005, 2006).

Soon after these features were discovered, however, an apparently contradictory aspect of the responses began to emerge, suggesting that focal visual stimuli cause cortical activity that spreads over time to a large region of cortex, appearing earlier in the retinotopically appropriate cortical locations and progressively later in more distal locations. This horizontal spread of neural activity constitutes a traveling wave. Traveling waves are evident in subthreshold potentials and are thus poised to influence the spike responses and thereby the output of area V1. They appear to work against the precise selectivity and orderly arrangement of V1 neurons along the cortical surface.

Here we review data that point to traveling waves as a prominent feature of area V1, both in the presence and in the absence of visual stimuli. We speculate briefly on the possible roles of these traveling waves in sensory processing and on the possible circuits underlying their propagation, and we discuss how the traveling waves can coexist with the crystalline precision of the cortex. The traveling waves constitute a mode of operation that is mostly engaged when visual stimuli are weak or absent. When a sufficiently high contrast is presented sufficiently often over a sufficiently large region, the waves disappear. In those conditions, primary visual cortex does operate in the highly selective and orderly fashion that had been described by Hubel and Wiesel.

We focus on traveling waves that propagate in the mammalian visual cortex, in the horizontal dimension, and at fairly high speeds (about 0.1–0.4 m/s). Other waves travel much slower, for instance, in binocular rivalry (~0.018 m/s; Lee et al., 2005) or in spreading depression (~0.00007 m/s; Lauritzen, 2001). We do not review the large literature on traveling waves in turtle cortex (Nenadic et al., 2003) or in nonvisual sensory or motor cortices of mammals (Ferezou et al., 2007; Fukunishi et al., 1992; London et al., 1989; Orbach et al., 1985; Reimer et al., 2011; Rubino et al., 2006; Wu et al., 2008). Moreover, we do not discuss waves that travel along the vertical dimension (Chauvette et al., 2010; Sakata and Harris, 2009). Finally, we do not review the literature on periodic oscillations (Ermentrout and Kleinfeld, 2001); the traveling waves that we discuss are periodic only when they are driven by periodic visual stimuli.

Waves Traveling across the Visual Field

The earliest evidence for traveling waves in primary visual cortex came from studies using single electrodes. These studies probed the effect of stimuli placed at varying distances from the receptive field of the recorded neurons and found that remote stimuli caused responses that were not only smaller but also more delayed. This effect was ascribed to travel of activity within cortex, and this view was supported by surgical manipulations.

Traveling waves can be observed in some of the earliest measurements of potentials obtained from the surface of V1 (Cowey, 1964). As one would expect, the largest potentials were obtained by placing the stimulus in the position that was retinotopically appropriate for the recording site; placing the stimulus further away elicited progressively smaller responses (Figure 1A). However, an additional intriguing property was seen: stimuli placed further away caused potentials that were progressively delayed (Figure 1A). Ablation of the cortex at the corresponding distal locations made the traveling activity disappear, suggesting that this activity was due to intracortical connections.

Similar results were obtained later in recordings of the local field potential (LFP) with penetrating electrodes (Ebersole and Kaplan, 1981). Again, placing the stimulus increasingly far from the retinotopic location of the recording site caused responses

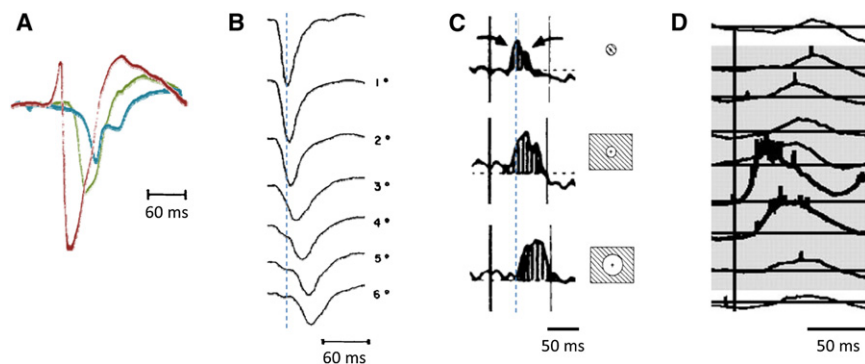


Figure 1. Recordings of Field Potential and Membrane Potential Suggest Traveling Waves

(A) Cortical surface potentials, measured from the foveal representation of area V1 in squirrel monkey. Stimuli are on the receptive field (red), ~3 deg away (green), and ~6 deg away (blue). Data are replotted from Figure 5 of Cowey (1964).

(B) Local field potential measurements from cat area V1. Stimuli are on the receptive field center (top) and on progressively more distant locations (bottom traces). Data are replotted from Figure 2 of Ebersole and Kaplan (1981).

(C) Current source density measurements obtained from the supragranular layer of cat area V1. Panels show the response to stimulus with diameter 12 deg, centered on the receptive field (top),

and to large stimuli sparing the central 12 deg (middle) or 24 deg (bottom). Data are replotted from Figure 5 of Mitzdorf (1985). (D) In vivo intracellular membrane potential measurements from cat area V1. Traces are responses to optimally oriented bars presented at varying distances from the receptive field center. Figure is modified from Figure 1 of Bringuier et al. (1999).

to become not only smaller but also more delayed (Figure 1B). As in the previous study, this traveling activity disappeared after ablation of the corresponding distal regions of primary visual cortex. This suggests that it is the circuitry of primary visual cortex that mediates the travel in activity.

More evidence suggesting traveling activity can be gleaned from early measurements of current source density (Mitzdorf, 1985). Current source density is thought to reveal the overall currents flowing into and out of neurons. Consistent with traveling activity, a localized stimulus elicits currents that have short latency, whereas stimulating more distal regions causes currents with longer latency (Figure 1C).

This early evidence for traveling activity across primary visual cortex received further support by studies that measured LFP elicited by stimuli presented over a whole array of spatial locations (Kitano et al., 1994). Robust LFP responses could be elicited by stimuli placed at surprisingly distal locations from the center of the receptive field, including locations in the ipsilateral visual field, which should elicit retinotopic responses only in the other hemisphere.

The interpretation of all of these field potential measurements was made much clearer by intracellular recordings of membrane potential (Bringuier et al., 1999). When a bar stimulus was flashed further away from the center of the receptive field, the membrane potential responses were not only reduced in amplitude but also markedly delayed in time (Figure 1D). The delay increased with increasing distance from the center of the cell's receptive field. This study provided strong evidence for traveling activity across the visual field and revealed that this activity depolarizes the neurons.

Waves Traveling across the Visual Cortex

The measurements of field potential and membrane potential that we have illustrated were made at a single point in cortex. Such measurements could prove the existence of activity moving across the visual field but could not demonstrate activity traveling across the cortex. A similar limitation would be encountered if one studied waves in a body of water based on the vertical displacement of a single buoy. Dropping stones in the water would cause displacements with a delay that depends on distance. However, to demonstrate that these are traveling

waves, one would need measurements from multiple buoys or, better, a series of images of the water.

In primary visual cortex, such parallel measurements became available thanks to advances in voltage-sensitive dye (VSD) imaging. The VSD signal reflects the summed subthreshold activity of neurons (and glia) with an emphasis on layer 2/3 (Grinvald and Hildesheim, 2004; Petersen et al., 2003a) and is therefore akin to massively parallel intracellular recording.

Early measurements made with VSD imaging in anesthetized monkeys revealed that a small visual stimulus activates a cortical region that is at first small and later progressively larger (Grinvald et al., 1994). This spreading activity covered a spatial extent of many mm (Figure 2A) and progressed at a speed of 0.10–0.25 m/s (0.08 m/s in Figure 2B).

Subsequent VSD imaging studies observed similar spreading activity in V1 of various species (Benucci et al., 2007; Chavane et al., 2011; Jancke et al., 2004; Roland et al., 2006; Sharon et al., 2007; Sit et al., 2009; Slovín et al., 2002; Xu et al., 2007). For instance, spreading activity was observed in awake monkeys (Slovín et al., 2002), in which a small and brief visual stimulus caused activity to grow progressively and expand over a diameter of at least 8 mm of visual cortex (Figures 2C and 2D).

Does the spreading activity constitute a traveling wave? The measurements of field potential and membrane potential reviewed earlier suggest that it is indeed traveling: the activity has a leading edge and a trailing edge, and both edges are delayed progressively with increasing distance (Figure 1). On the other hand, the VSD responses seem more similar to a standing wave, one in which the amplitude depends on time but the spatial footprint remains fairly constant over time (Figure 2D).

Evidence in favor of traveling activity came from a VSD imaging study that measured V1 responses to small stimuli reversing periodically in contrast (Benucci et al., 2007). These stimuli caused VSD signals that oscillated at twice the reversal frequency, consistent with the view that VSD signals in area V1 reflect mostly the activity of complex cells. The frequency-doubled oscillation appeared earliest in the retinotopic location of the stimulus and was clearly delayed as it progressed to more distal locations in cortex (Figure 3A).

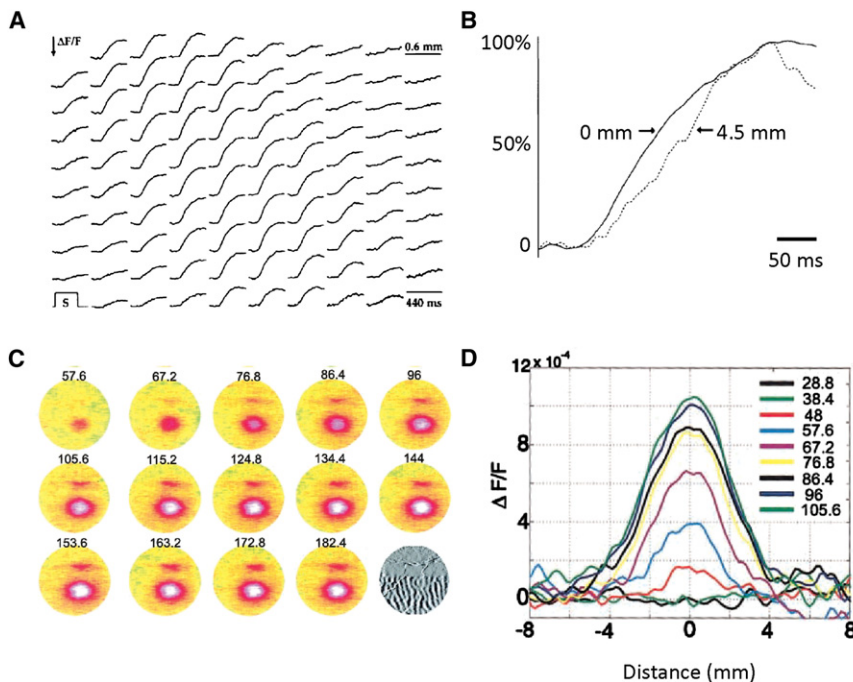


Figure 2. VSD Imaging Reveals Spreading Activity on Cortical Surface

(A) Time courses of VSD responses in V1 of an anesthetized monkey, measured at an array of locations covering 6×6 mm. The stimulus was a small grating flashed for 250 ms.

(B) Time courses at two locations, one in the retinotopic location of the stimulus and the other 4.5 mm away. Responses are scaled to peak at the same height to illustrate delay of ~ 60 ms between them. Data are from Figures 7 and 10 of Grinvald et al. (1994).

(C) Spread of activity in area V1 and V2 of awake monkey, measured at various times after the onset of a small visual stimulus. The large response is in V1 and the smaller response above it is in V2. The V1/V2 boundary is delineated by the map of ocular dominance at the bottom right.

(D) Spatial profiles measured through axis parallel to the V1/V2 border, at different time points. Data are from Figures 8 and 9 of Sloviter et al. (2002).

These measurements allowed precise estimates of the speed of propagation of the traveling waves across the cortex (Figures 3B and 3C). Periodic responses yield robust estimates of amplitude and phase (they are just two numbers, obtained from thousands of data points). The phase is a measure of delay, and by suitable spatial averaging it could be computed even in distal locations, where responses had extremely low amplitude. Delay grew linearly with distance in cortex, with a slope of 0.3 m/s (Figure 3C).

This traveling speed is broadly consistent with the speed estimated from intracellular recordings (Bringuier et al., 1999). These recordings yielded deflections in membrane potential (Figure 1D) from which amplitude and delay could be readily obtained (Figures 3D and 3E). The most common speed of propagation was ~ 0.1 deg/ms, but faster speeds were also common. Since the magnification factor was ~ 1 mm/deg, these speeds in the visual field correspond to speeds in cortex that were often faster than ~ 0.1 m/s.

Overall, the cortical dynamics observed in these studies are consistent with a traveling wave. Specifically, they indicate that the activity elicited by a localized stimulus spreads to a large region of cortex, appearing earlier in the retinotopically appropriate cortical locations and progressively later in more distal locations. This activity is inconsistent with a standing wave, one that grows in amplitude with constant footprint (Benucci et al., 2007).

However, the traveling waves do not simply have a constant profile that is translated at a constant velocity. For instance, the wave is markedly dampened with distance (Figure 3B). Moreover, we will see that velocity can depend on time or amplitude of response, with the peak of the wave traveling slower than the leading and trailing edges. Finally, there are indications that velocity can depend on space. VSD imaging of rat V1 revealed

that traveling waves caused by focal visual stimulation undergo stereotyped distortions (Xu et al., 2007). Waves initiated in V1 decelerated and compressed as they moved toward the border with the next visual area. Upon hitting this border, the waves propagated further but were also reflected back into V1.

Some of these effects may be specific to the rat visual cortex under anesthesia. For instance, in monkey visual cortex, a small stimulus evokes distinct activations in areas V1 and V2, with subsequent spread in all directions and not specifically toward the V1/V2 border (Figure 2C). Perhaps the waves of activity seen when the cortex is in a synchronized state (as may be the case in the anesthetized rat, Harris and Thiele, 2011) are qualitatively different from the concentric waves caused by visual activation in a desynchronized cortex (as would be expected in an alert monkey). Nonetheless, these disparate observations remind us that we know only little about the interaction between traveling waves and cortical architecture.

Traveling Waves below and above Threshold

The demonstrations of traveling waves that we have discussed all involved measurements of subthreshold activity, either in the membrane potential of individual neurons or in the mass subthreshold activity of neuronal populations, gauged from field potential recordings and from VSD imaging. The depolarization seen in the subthreshold responses is consistent with the traveling wave being facilitatory, thus increasing the probability of a spike above baseline. One might ask, then, if traveling waves are also present in the spike responses.

An initial answer to this question can be gleaned from the intracellular measurements (Bringuier et al., 1999). In the example traces, robust spike responses could be obtained from only two locations in the center of the receptive field (Figure 1D). Nonetheless, more distal stimuli did elicit occasional spikes, with a latency that does seem to grow with increasing distance.

By averaging the responses through enough stimulus presentations, indeed, one can see clear traveling waves of spiking

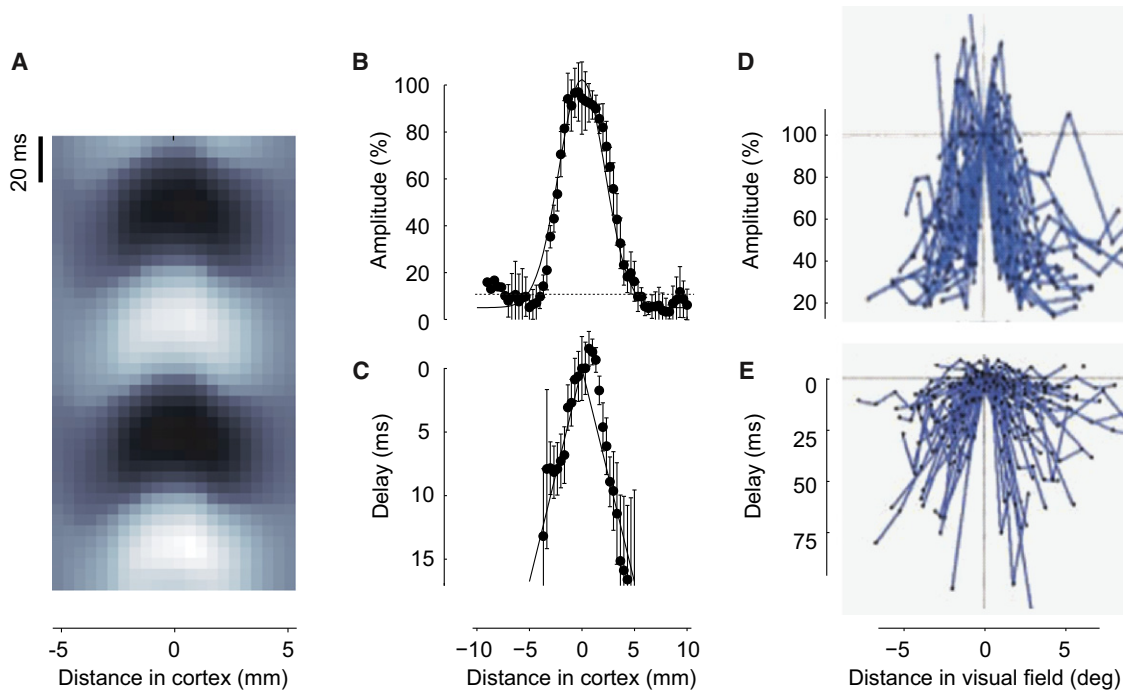


Figure 3. The Spreading Activity Is a Dampened Traveling Wave

(A) Propagating wave measured over the cat visual cortex in response to a contrast-reversing focal stimulus. The intensity indicates the average VSD signal as a function of distance from the retinotopic location of the stimulus and of time.

(B and C) Amplitude (B) and phase (C) of the second harmonic response as a function of cortical distance. Figure is adapted from Figure 6 of [Benucci et al. \(2007\)](#). (D and E) Amplitude (D) and delay (E) of traveling waves in membrane potential, measured intracellularly. Abscissa is expressed in degrees of visual angle by undoing the conversion to mm of cortex that had been applied in the original study. Figure is modified from Figures 2 and 4 of [Bringuier et al. \(1999\)](#).

activity (Figure 4). We illustrate this effect by analyzing responses of cat area V1 to bars presented in random positions. As expected, the LFP responses described a clear traveling wave, with latency increasing progressively with distance between the stimulus and the center of the receptive field (Figures 4A and 4B). Also as expected, spike responses (Figure 4D) were more highly localized than LFP responses, with a space constant of 2.7 deg (Figure 4F) versus 4.2 deg (Figure 4C). Indeed, LFP signals reflect subthreshold responses, which can be elicited from a larger area of visual field than spikes ([Bringuier et al., 1999](#)). Even though spike responses to distal visual stimuli were weak, however, the extensive averaging involved in this analysis reveals a delay that grows progressively with distance (Figure 4E).

These analyses reveal that localized visual stimuli elicit traveling waves not only in subthreshold responses but also in spikes. The traveling waves, however, die off after a shorter distance in spikes than they do in subthreshold responses. This makes it harder to observe traveling waves in spiking activity and perhaps explains why traveling waves seem to have escaped the attention of Hubel and Wiesel and of subsequent studies that measured spike responses in area V1.

Traveling Waves in Spontaneous Activity

The visual cortex is active even in the absence of visual stimuli. There is substantial interest in studying this ongoing activity, as it is believed to reflect the basic organization of the cortical

circuitry ([Arieli et al., 1995, 1996](#); [Destexhe and Contreras, 2006](#); [Haider and McCormick, 2009](#); [Kenet et al., 2003](#); [Ringach, 2009](#); [Tsodyks et al., 1999](#)). An important feature in ongoing activity seems to be the presence of traveling waves.

VSD imaging of ongoing activity in a large portion of mouse cortex under anesthesia revealed wide planar waves, which are mostly symmetrical in the two hemispheres ([Mohajerani et al., 2010](#)). These waves seem to show little regard for borders between areas: they invest area V1 just as much as other cortical areas. The waves may be related to the slow and somewhat periodic oscillation that is seen in the cortex of animals under anesthesia, during non-REM sleep, or in quiet wakefulness ([Petersen et al., 2003b](#); [Sakata and Harris, 2009](#); [Steriade et al., 1993](#)). This oscillation may be a feature of synchronized cortical states ([Harris and Thiele, 2011](#)), and it is known to spread as a traveling wave along the cortical surface ([Petersen et al., 2003b](#)).

Recordings of ongoing activity with electrode arrays have revealed an additional kind of traveling wave, organized concentrically around spiking neurons. These waves were measured in V1 of anesthetized cats and monkeys, by averaging the LFP at each electrode, triggered on spikes measured at a designated electrode ([Nauhaus et al., 2009](#)). The resulting spike-triggered average of the LFP was a traveling wave that was stereotyped, regardless of triggering location (Figure 5A). The wave was largest at the triggering location and progressively smaller and increasingly delayed at more distant locations

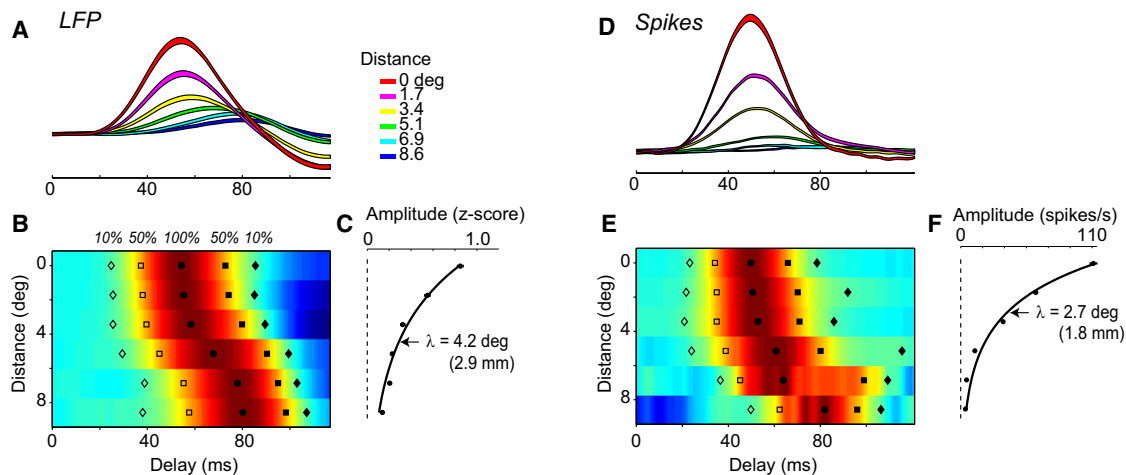


Figure 4. Traveling Waves in Field Potential and in Spikes

Data from a recording in cat V1 used in a prior study (Busse et al., 2009). The visual stimulus was a rapid sequence of bars, each shown for 32 ms at a random position, orientation, and spatial phase. Randomly interleaved blank stimuli were used to measure baseline activity, which was then subtracted from all responses. Data are averaged across 69 sites in a 10×10 array, selected because they gave both clear LFP responses and clear multiunit spike responses. For each site, we considered LFP and spike responses to the bars having the optimal orientation for the site.

(A) Average time course of the LFP (filtered between 1–200 Hz and Z scored) for multiple stimulus distances from the receptive field center (legend). The width of each trace indicates 2 SE ($n = 69$).

(B) Heat map of the LFP responses, each normalized by peak amplitude. Symbols indicate various time points during rising and falling edges, as indicated.

(C) Amplitude of the traces in (A) as a function of distance. Curve is best fitting exponential, and arrow indicates its space constant λ (expressed in deg of visual angle and in the corresponding mm of cortex at this eccentricity).

(D–F) Same as (A)–(C) but for the multiunit spike responses measured simultaneously in the same sites. Spike trains were smoothed with a Gaussian window ($\sigma = 4$ ms).

(Figures 5B and 5C). This result is consistent with the idea that spikes in one location generate depolarizations that are progressively weaker and more delayed at increasing distances from the spike site.

Various aspects of these results were later challenged by a study performed in awake monkeys (Ray and Maunsell, 2011). This study argued that the spike-triggered LFP was best described by a sum of standing waves, not by traveling waves. However, a debate ensued (Nauhaus et al., 2012), and it was argued that at least one of the two data sets obtained in the awake monkeys shows clear evidence for traveling waves (Figures 5D and 5E). This observation seems to suggest that spike-triggered traveling waves are a robust phenomenon, present not only under anesthesia but also in the alert brain.

The concentric traveling waves revealed by spike triggering (Figure 5) may be fundamentally different from the wide planar traveling waves seen in conditions such as non-REM sleep. A possible analogy to illustrate this difference relies once again on the metaphor of waves in a body of water. When it rains, the deflections on the water are caused by two kinds of wave: simultaneous concentric waves caused by the raindrops (similar to those seen with spike triggering) and planar waves caused by the wind (similar to those seen in large organized ongoing activity).

However, this metaphor is not perfect: whereas waves in a body of water cannot influence the subsequent raindrops, waves in membrane potential can certainly influence subsequent spikes. Moreover, there might not be such a fundamental difference between the waves measured by spike triggering and other dynamics of ongoing activity. For instance, it is possible that planar waves moving in random directions could

give rise to apparently concentric waves once one measures them by spike triggering. This is an area that requires further research.

Context Dependence of Traveling Waves

A remarkable feature of traveling waves in primary visual cortex is that they depend on visual context. The waves are evident in response to small localized stimuli (Figures 1, 2, 3, and 4) and during ongoing activity (Figure 5). In the presence of strong stimulation over a large region of the visual field, however, the waves are greatly reduced.

Early evidence for this dependence of spatial propagation on visual context comes from measurements of LFP from a single electrode (Kitano et al., 1994). The stimulus in this study was composed of small patches of grating reversing in contrast independently of each other. If shown simultaneously, these patches covered a vast region of visual field. The response elicited by each patch was measured by triggering the LFP on contrast reversal in that patch. This experiment was run in two ways: one patch at a time and all patches together. In the first case, LFP responses could be elicited from stimuli as far as 15 deg from the receptive field center (Figure 6A). In the second case, instead, LFP responses were elicited only by one patch, with a short latency (Figure 6B). By subtracting the responses obtained in the two conditions, the authors identified a “slow distributed component” that is present only when the stimulus is localized (Figure 6C). They ascribed this component to propagation of activity across the cortical surface.

Further evidence for the dependence of spatial propagation on visual context came from recordings with electrode arrays

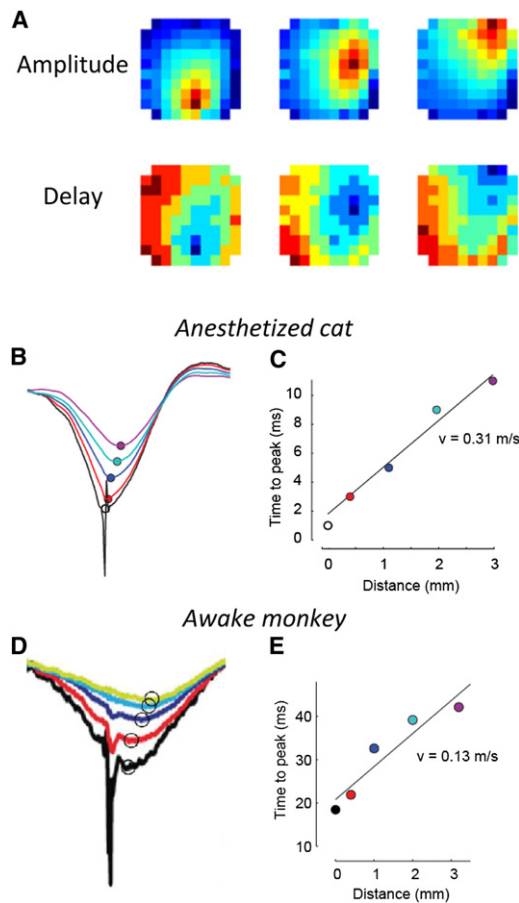


Figure 5. Traveling Waves in Spontaneous Activity
LFP signals measured by a 10×10 electrode array are spike triggered with one electrode as the reference site for spiking activity.
(A) Amplitude and delay for three triggering locations in anesthetized monkey. Figure is adapted from Figure S3 in Nauhaus et al. (2009).
(B) Spike-triggered LFP traces measured in anesthetized cat.
(C) Time to peak of these traces is longer at more distant recording locations. Figure is adapted from Figure 2 of Nauhaus et al. (2012).
(D and E) The same as (B) and (C) with data from awake monkey, as recorded by Ray and Maunsell (2011) and replotted in Figure 4 of Nauhaus et al. (2012).

(Nauhaus et al., 2009, 2012). As we have seen, the spike-triggered LFP measured with these arrays during spontaneous activity constitutes a traveling wave (Figures 5 and 6D). When the same spike-triggered analysis was performed on responses to large full-contrast gratings, instead, the results were strikingly different (Figures 6E and 6F). First, the wave amplitude was much reduced (by an average factor of 2.2). Second, the spatial extent covered by the waves was substantially smaller (by an average factor of 4.2). Measurements performed at intermediate contrasts gave intermediate results.

These results are consistent with the known tendency for visual cortex to be more noisy and correlated when the strength of visual stimulation is reduced. Indeed, decreasing contrast increases the trial-to-trial variability in the inputs to V1 neurons (Finn et al., 2007) and the correlated response variability among pairs of neurons (Kohn and Smith, 2005). Whereas the activity driven by strong and extended visual stimuli reflects largely

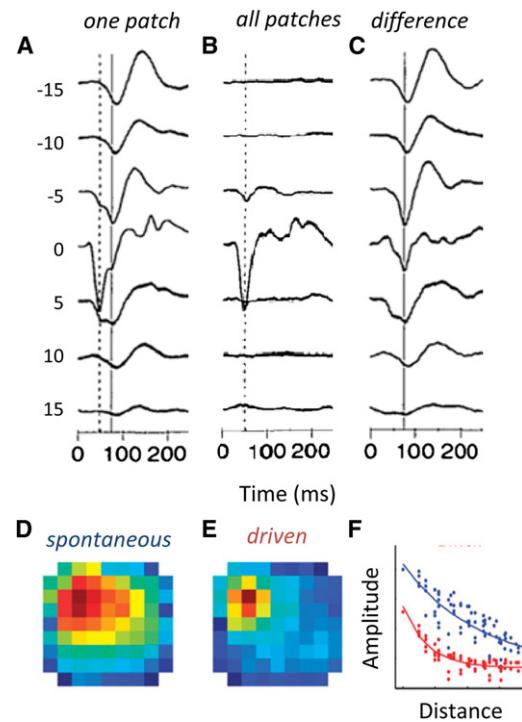


Figure 6. Context Dependence of Traveling Waves
(A) LFP responses measured from a single electrode in cat visual cortex, in response to a contrast-reversing grating at seven different stimulus positions. Time zero is the time of reversal.
(B) Same as (A), while the grating is surrounded by a large number of other gratings that is reversing in contrast independently.
(C) Difference between the traces in (A) and (B). Figure is modified from Figure 7 of Kitano et al. (1994).
(D) Amplitude of spike-triggered LFP measured during spontaneous activity with an electrode array of 10×10 in monkey area V1 (same as Figure 5A).
(E) Same as (D), measured while responses are driven by a large, high-contrast grating.
(F) Amplitude and spatial spread are larger in spontaneous condition. Data are from Figure 5 of Nauhaus et al. (2009).

local computations, spontaneous activity is dominated by global fluctuations and traveling waves.

Once again, we can visualize some of these results using the analogy of raindrops falling on a body of water: it is as if increasing contrast in a large region of space progressively increased the viscosity of the water, making it resemble oil. Indeed, a raindrop falling on oil would make small traveling waves, which would propagate only over short distances.

Possible Roles of Traveling Waves

The traveling waves seem to be fundamentally at odds with the main view of V1 neurons as a set of highly selective local filters. Indeed, after establishing a crystalline selectivity for attributes such as stimulus orientation and position, why go corrupt this selectivity with lateral inputs? The results reviewed in the last section may help lead to an answer. The traveling waves constitute a mode of operation that is mostly engaged when visual stimuli are weak or absent. When a sufficiently high contrast is distributed over a sufficiently large region, the waves disappear.

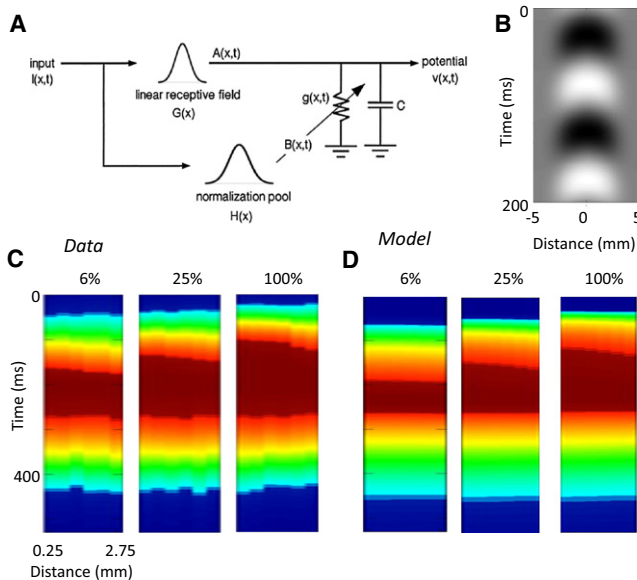


Figure 7. A Possible Relationship between Traveling Waves and Divisive Normalization

(A) The normalization model implemented with a resistor-capacitor circuit. Signals in the numerator come from the spatial “receptive field” and signals from the denominator from a “normalization pool.”

(B) A simulation of the traveling wave observed by *Benucci et al.* (2007) in response to contrast-reversing stimulation (Figure 3A).

(C) Responses of monkey V1 to a small grating presented for 200 ms, as a function of time (ordinate) and distance from the center of the stimulated region (abscissa). Each column corresponds to a stimulus contrast. Colors represent percentiles of the maximal response, with cyan marking response onset and offset.

(D) Fits of the normalization model to these data. Data are from Figures 2, 5, 6 and Figure S4 of *Sit et al.* (2009).

The profound dependence of traveling waves on visual contrast constrains their possible functional roles. For instance, it was proposed that the traveling waves serve to process visual motion (*Seriès et al.*, 2002). This proposal appears reasonable because the waves represent a temporal progression of activity over visual space. However, it seems unlikely that mechanisms of motion processing should work best at the lowest contrasts and worst at high contrast.

The contrast dependence of the waves, instead, seems more consistent with phenomena of long-range interactions across stimuli. Such interactions are typically revealed by placing a stimulus on the center of a neuron’s receptive field and another stimulus in a more displaced location. The effect of the second stimulus is often suppressive, as in “surround suppression” and “size tuning” (*Carandini*, 2004; *Fitzpatrick*, 2000). In other cases, however, the lateral interactions are facilitatory. This facilitation has been proposed to mediate integration of stimuli across receptive fields (*Gilbert*, 1992; *Kapadia et al.*, 1999; *Polat et al.*, 1998) or more prosaically to build individual receptive fields (*Angelucci and Bressloff*, 2006; *Angelucci et al.*, 2002; *Cavanaugh et al.*, 2002a).

Traveling waves seem ideally poised to participate in facilitatory long-range stimulus interactions. First, they cover large regions of space. Second, they are largely facilitatory (they

depolarize neurons and cause spikes). Third, they are partially selective for orientation (as we will see shortly). Fourth, they disappear when there is high contrast in a large region of visual space. However, it is not known whether these facilitatory interactions take time to arrive to neurons—as waves do. Future experiments could test this prediction by eliciting traveling waves via multiple concurrent stimuli.

Traveling waves might also participate in suppressive stimulus interactions, if such interactions are due to withdrawal of facilitation. The common view of surround suppression is that it is mostly due to intracortical inhibition (*Haider et al.*, 2010). However, others think that it operates through withdrawal of intracortical excitation (*Ozeki et al.*, 2009). Perhaps intracortical excitation amplifies maximally the responses to stimuli that are small and have low contrast, and surround suppression is a loss in this amplification. The traveling waves may reflect this amplification, and their disappearance at high contrast would be synonymous with the appearance of surround suppression.

To summarize, perhaps traveling waves participate both in facilitation (through their presence) and in suppression (through their absence). Indeed, long-range stimulus interactions turn from overall facilitatory at low contrast to overall suppressive when there is high contrast in a large region of visual space (*Cavanaugh et al.*, 2002a; *Kapadia et al.*, 1999; *Polat et al.*, 1998; *Sceniak et al.*, 1999).

This idea is in line with the normalization model, a quantitative framework that can describe both facilitatory and suppressive stimulus interactions. In the model, the responses of neurons result from a division: in the numerator, there are signals from a region of space that drive the neuron, and in the denominator, there is a constant plus the signals from the normalization pool (*Carandini and Heeger*, 2012). If the regions of space driving the numerator and denominator are suitably wide, normalization accounts for multiple aspects of long-range stimulus interactions (*Bonin et al.*, 2005; *Cavanaugh et al.*, 2002b; *Chen et al.*, 2001; *Schwartz and Simoncelli*, 2001). When overall contrast is high, the signals in the denominator reduce gain and limit the extent of spatial integration. Conversely, when overall contrast is low, the signals from the normalization pool are small relative to the constant in the denominator and do little to reduce gain and limit spatial integration.

Indeed, an imaging study showed that the traveling waves are well described by a common implementation of the normalization model (*Sit et al.*, 2009). This study used VSD imaging to measure V1 responses to a small, briefly flashed stimulus (Figure 7). The time to peak of these responses was progressively delayed at greater distances from the center of activation, consistent with a traveling wave (Figure 7C). These data were fit by a version of the normalization model in which the divisive interaction is mediated by a resistor-capacitor circuit (Figure 7A). Increasing the conductance of this circuit causes not only a divisive reduction of response gain but also a shortening of response latency (*Carandini and Heeger*, 2012). This effect is largest at the center of the stimulated region, where local contrast is highest. The responses at the center therefore rise at a faster rate than those at the periphery. This prediction matched the data fairly closely (Figure 7D).

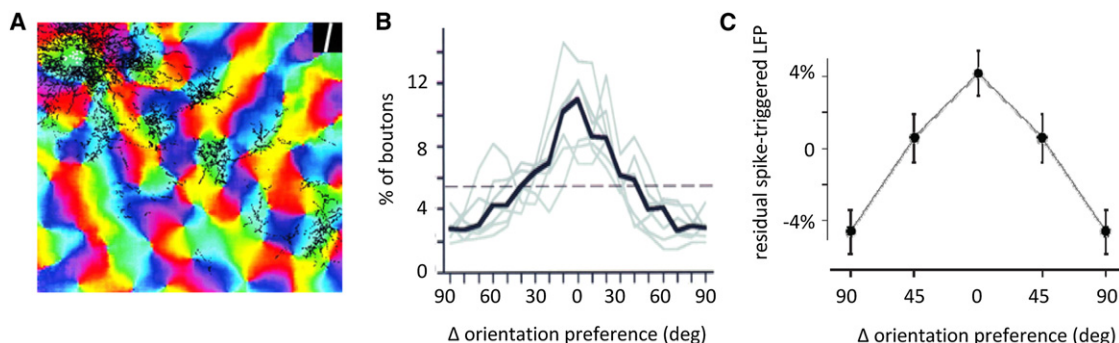


Figure 8. Horizontal Connections between Sites with Similar Orientation Preference

(A) Anatomical demonstration of horizontal connections in tree shrew visual cortex. A site on the top left of the image was injected with biocytin (an anterograde tracer), and the stained synaptic boutons are shown overlaid with the map of orientation preference.

(B) Distribution of orientation preference of synaptic boutons. Difference in orientation preference between the injected sites and the sites of boutons are measured. Data are from Figures 4 and 6 of Bosking et al. (1997).

(C) Bias for orientation of traveling waves seen during ongoing activity in cat visual cortex, after the main effect of distance (Figure 5) has been removed. The amplitude of spike-triggered LFP is larger in sites with similar orientation preference. Data are from Figure 4 of Nauhaus et al. (2009).

Two attributes of these responses, however, appear to be different from simple traveling waves. In a simple traveling wave, all aspects of the waveform shift coherently with cortical distance. In the data of Sit et al. (2009), instead, both the very onset (e.g., the rise to 10% of peak) and the offset of the responses appear to be independent of distance (Figure 7C). The normalization model captured these effects (Figure 7D) because before stimulus onset and after stimulus offset the contrast is zero everywhere, so the normalization pool gives the same signal (zero) at all locations.

According to the model, the key feature that determines traveling activity is overall contrast, i.e., the value and distribution of contrast over a large region of visual space. If overall contrast is on average high, as with stimuli reversing rapidly in contrast, then the model predicts a traveling wave in both the leading edge and the trailing edge (Figure 7B), just as observed in the data (Figure 3A). However, it is not clear that overall contrast could be considered constant in all the experiments that have demonstrated travel both in the leading edge and in the trailing edge (Figure 1). Moreover, the normalization model may be a useful summary of the phenomena of traveling waves but does not by itself constitute a functional role nor does it reveal the underlying biophysical mechanisms (Carandini and Heeger, 2012). Specifically, assigning signals to the numerator or to the denominator is not equivalent to assigning them to specific circuits (e.g., thalamocortical versus intracortical).

Possible Mechanisms of Traveling Waves

Are the traveling waves that are observed in V1 due to circuitry present within cortex? One implementation of the normalization model suggests that they are not (Sit et al., 2009) and that rather they are due to appropriately delayed activity in lateral geniculate nucleus (LGN). However, this feedforward implementation is unlikely to be realistic, because the waves have not been reported in the firing of LGN neurons and because the LGN has projection zones into V1 that are much smaller than the extent of propagation of the waves. For instance, in

cat, the diameter of LGN projections to V1 ranges between 0.8 and 1.4 mm (Freund et al., 1985; Humphrey et al., 1985; Jin et al., 2011), and the scatter of V1 receptive fields is relatively modest (Hetherington and Swindale, 1999), making it hard to explain activity that spreads over 4–5 mm of cortex (Figure 3B). Similarly, in monkey, the projection zones of LGN into V1 are much smaller than the extent of propagation of the waves (Angelucci and Sainsbury, 2006; Blasdel and Lund, 1983).

This leaves open two possibilities: the waves could arise from circuitry present within area V1 or they may rely on inputs from higher visual areas. The latter possibility seems attractive at first, because neurons in some higher area could have vast receptive fields and might perhaps send feedback that is increasingly delayed to regions of V1 that are increasingly distal in terms of retinotopy. However, robust waves were seen in animals that were deeply anesthetized, and, in this condition, it is hard to imagine that higher visual areas would respond reliably.

It seems wise and parsimonious, therefore, to first seek the causes of traveling waves within the circuitry of V1 itself. A natural candidate for the traveling waves within V1 is provided by the long-range horizontal connections that have been observed in multiple species (Bosking et al., 1997; Creutzfeldt et al., 1977; Finken et al., 1975; Gilbert and Wiesel, 1979; Rockland and Lund, 1982). Horizontal connections extend over many millimeters of visual cortex (Figure 8A) and propagate activity at speeds that are comparable to those observed in traveling waves. For instance, an in vitro study of propagation of activity along horizontal connections in cat V1 reported a speed of 0.3 m/s (Hirsch and Gilbert, 1991), comparable to the speed of the traveling waves that we have reviewed.

A test of the relationship between horizontal connections and traveling waves lies in their dependence on preferred orientation. Some anatomical studies (e.g., Bosking et al., 1997) indicate that horizontal connections tend to link preferentially sites with similar orientation preference (Figures 8A and 8B). Intriguingly, a similar effect is seen in traveling waves during ongoing activity (Nauhaus et al., 2009): the waves have a slight bias for regions with similar orientation preference as the triggering site

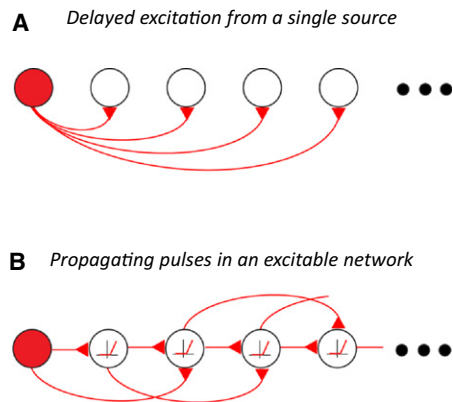


Figure 9. Possible Network Scenarios Giving Rise to Traveling Waves

Filled circles indicate wave sources. Open circles are local elements (a neuron or a group of neurons) that receive subthreshold inputs.

(A) A model in which wave is simply generated in a single location and transmitted passively to other locations.

(B) A model with regenerative process. Schemata inside elements indicate a stage of rectification: these elements signal to the other elements only once activity passes a threshold. Figure is inspired by Figure 1 in Prechtl et al. (2000).

(Figure 8C). Moreover, a similar selectivity for orientation is seen in traveling waves evoked by visual stimuli, especially in the cortical locations near the retinotopic representation of the stimulus (Chavane et al., 2011). This selectivity for orientation supports the view that the waves travel along horizontal connections.

Indeed, horizontal connections have been implicated in traveling waves also in other sensory cortices (Wu et al., 2008), where they show similar biases. Waves in rodent barrel cortex, for instance, travel twice as fast along the rows than along the arcs (Derdikman et al., 2003; Petersen et al., 2003a), and this bias matches a bias in the axons of layer 2/3 pyramidal neurons, which extend preferentially along the rows (Petersen et al., 2003a). Skewed propagation has also been reported in primary auditory cortex, where tone-evoked activity spreads preferentially within an isofrequency strip (Song et al., 2006). Again, this spread may reflect the axonal distribution of layer 2/3 pyramidal neurons, which is biased to the isofrequency axis (Matsubara and Phillips, 1988).

There are two principal scenarios by which horizontal connections could cause traveling waves (Prechtl et al., 2000). The first scenario involves delayed excitation from a single source (Figure 9A): the spiking neurons at the source of the wave would send horizontal connections to multiple other locations, causing subthreshold excitation in the target neurons. These neurons do not need to spike for the wave to go further. The second scenario involves propagating pulses in an excitable network (Figure 9B). In this scenario, the excitatory connections need not reach as far, but the intermediate neurons (or at least some of them) do need to fire for the wave to go further. Every wave that requires a regenerative process can be categorized in the second scenario.

One way to discern among these scenarios is based on speed. Waves in the second scenario might propagate slower than in the first scenario, as activity may have to reverberate in a local

group of neurons before it becomes strong enough to progress to the next location. This regeneration requires multiple synaptic delays and multiple stages of cellular integration, which all add to the delays imposed by axonal propagation.

Examples of waves that are likely to follow the second scenario are the Up and Down oscillations seen when the cortex is in the synchronized state (Harris and Thiele, 2011; Petersen et al., 2003b; Steriade et al., 1993). These oscillations travel markedly slower than axonal propagation, with a typical speed below 0.1 m/s. Consistent with the second scenario, moreover, in these waves, activity spreads not only in subthreshold responses but also in suprathreshold spike responses. The importance of regenerative excitatory processes in these slow waves is indicated by experiments in vitro, in which focal AMPA receptor blockers markedly slow down the waves (Compte and Wang, 2006; Golomb and Amitai, 1997; Pinto et al., 2005) or even stop the waves altogether (Sanchez-Vives and McCormick, 2000). In the first scenario, these manipulations could not have these effects. However, horizontal connections are still likely to be involved, as network simulations suggest that they are crucial to reproduce these findings (Compte et al., 2003).

The traveling waves elicited by a flashed bar in cat visual cortex, instead, seem to fall in the first scenario. Spike activity are largely confined to the retinotopic region representing the stimulus (Bringuier et al., 1999) (see also Figure 4), so the wave sources are not regenerated in the neighboring regions. Rather, the waves appear to be caused by monosynaptic inputs from a single source and to propagate at the speed of axonal propagation. Indeed, we have seen that the wave speed measured in vivo (0.10–0.35 m/s) is consistent with the axonal propagation velocity measured in vitro (0.3 m/s, Hirsch and Gilbert, 1991).

On the other hand, it is challenging to explain the context dependence of traveling waves (Figure 6) in the first scenario. Horizontal connections are present regardless of context, so it is not obvious that their effects would disappear in conditions of high overall contrast. A promising avenue of research in this respect concerns neuromodulators such as acetylcholine, which may play a role in determining the relative strength of thalamocortical inputs versus lateral inputs (Gil et al., 1997) and consequently the spread of activity in visual cortex (Silver et al., 2008).

Finally, though there is little doubt that the waves propagate via synaptic excitation, it appears that synaptic inhibition is crucial to contain them. In barrel cortex in vivo, indeed, blocking GABA_A receptors with bicuculline markedly increased the spread of propagating waves (London et al., 1989; Orbach et al., 1985). Similar observations were made in vitro (Chagnac-Amitai and Connors, 1989; Petersen and Sakmann, 2001; Pinto et al., 2005). These results indicate that GABAergic inhibition controls the spatial extent of traveling waves. GABAergic inhibition, therefore, may be involved in the marked context dependence of traveling waves in visual cortex (Figure 6). The role of GABA in traveling waves, however, is not currently understood and neither is the possible role that might be played by long-range GABAergic projections (Higo et al., 2007; McDonald and Burkhalter, 1993; Tomioka et al., 2005).

Future Directions

In reviewing the evidence in favor of traveling waves in primary visual cortex, we have identified multiple questions that remain unanswered. Perhaps the main one concerns the relationship between different kinds of traveling waves. Our Review has focused on concentric waves evoked by focal stimuli (Figures 2, 3, 4, and 6) and seen in ongoing activity (Figure 5), but we have also mentioned large planar waves that are seen especially during non-REM sleep. What is the relationship between these kinds of waves, and do they share the same mechanisms? Also, there are other kinds of propagating activity, such as spiral waves (Huang et al., 2010), and future work needs to clarify the relationships and differences among them.

In fact, while we have not hesitated in using the term “traveling wave” to describe the dynamics of activity across space and time, others might disagree with us. We have reviewed substantial evidence supporting the notion that focal visual stimuli cause cortical activity that spreads over time to a large region of cortex, appearing earlier in the retinotopically appropriate cortical locations and progressively later in more distal locations. We believe that it is useful to describe all this as a traveling wave. However, we have also reviewed data (Figure 7) in which some aspects of activity do not seem to show any travel (Sit et al., 2009). Based on these aspects, one might hesitate to refer to the dynamics of activity as a traveling wave.

Future experiments could address these questions and ideally go beyond the representation of single waves originating in single places. By using more than one stimulus (but not too many, otherwise, as we have seen the waves disappear), one could characterize how waves interact with each other, and how they relate to the interactions between stimuli that have been extensively documented. Specifically, it would be very useful to establish whether the waves are indeed related to phenomena of long-range facilitation or suppression, e.g., by studying the time course and spatial extent of these phenomena with imaging. Addressing these questions would go a long way toward establishing the possible functional roles of the traveling waves, which overall remain rather mysterious.

To establish these functional roles, furthermore, it would be ideal to measure them during the performance of a visual task. In doing so, it might be possible to relate them to percepts on a trial-by-trial basis or at least to relate their presence to overall properties of the task. For instance, an appealing (but unproven) role of the waves may be one of pooling information over space to deal with measurement noise. Perhaps V1 needs to integrate over a large region of space at low contrast—when noise would have the largest impact—and obtain higher spatial resolution at high contrast—when noise is much less of an issue. Psychophysical measurements, especially if performed while the traveling waves are being imaged, could begin to test these ideas.

Additional questions concern the mechanisms of propagation of the waves and the flexibility that these mechanisms would need to display to account for the properties of the waves. Optogenetic manipulation of specific circuit elements may allow us to achieve these goals (Tye and Deisseroth, 2012) and so would the improvement in genetically encoded neural activity indicators such as calcium sensors and voltage sensors (Akemann et al., 2010; Looger and Griesbeck, 2012). Paired

with well-established techniques of visual stimulation and recording, these new methods appear to be ideally suited to unravel the mysteries of traveling waves and their perceived inconsistency with the otherwise crystalline organization of the primary visual cortex.

ACKNOWLEDGMENTS

This work was supported by the Medical Research Council (grant G0800791) and by the European Research Council (project CORTEX). M.C. holds the GlaxoSmithKline / Fight for Sight Chair in Visual Neuroscience.

REFERENCES

- Akemann, W., Mutoh, H., Perron, A., Rossier, J., and Knöpfel, T. (2010). Imaging brain electric signals with genetically targeted voltage-sensitive fluorescent proteins. *Nat. Methods* 7, 643–649.
- Angelucci, A., and Bressloff, P.C. (2006). Contribution of feedforward, lateral and feedback connections to the classical receptive field center and extra-classical receptive field surround of primate V1 neurons. *Prog. Brain Res.* 154, 93–120.
- Angelucci, A., and Sainsbury, K. (2006). Contribution of feedforward thalamic afferents and corticogeniculate feedback to the spatial summation area of macaque V1 and LGN. *J. Comp. Neurol.* 498, 330–351.
- Angelucci, A., Levitt, J.B., Walton, E.J., Hupe, J.M., Bullier, J., and Lund, J.S. (2002). Circuits for local and global signal integration in primary visual cortex. *J. Neurosci.* 22, 8633–8646.
- Arieli, A., Shoham, D., Hildesheim, R., and Grinvald, A. (1995). Coherent spatiotemporal patterns of ongoing activity revealed by real-time optical imaging coupled with single-unit recording in the cat visual cortex. *J. Neurophysiol.* 73, 2072–2093.
- Arieli, A., Sterkin, A., Grinvald, A., and Aertsen, A. (1996). Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. *Science* 273, 1868–1871.
- Benucci, A., Frazor, R.A., and Carandini, M. (2007). Standing waves and traveling waves distinguish two circuits in visual cortex. *Neuron* 55, 103–117.
- Blasdel, G.G., and Lund, J.S. (1983). Termination of afferent axons in macaque striate cortex. *J. Neurosci.* 3, 1389–1413.
- Bonin, V., Mante, V., and Carandini, M. (2005). The suppressive field of neurons in lateral geniculate nucleus. *J. Neurosci.* 25, 10844–10856.
- Bosking, W.H., Zhang, Y., Schofield, B., and Fitzpatrick, D. (1997). Orientation selectivity and the arrangement of horizontal connections in tree shrew striate cortex. *J. Neurosci.* 17, 2112–2127.
- Binguier, V., Chavane, F., Glaeser, L., and Frégnac, Y. (1999). Horizontal propagation of visual activity in the synaptic integration field of area 17 neurons. *Science* 283, 695–699.
- Busse, L., Wade, A.R., and Carandini, M. (2009). Representation of concurrent stimuli by population activity in visual cortex. *Neuron* 64, 931–942.
- Carandini, M. (2004). Receptive fields and suppressive fields in the early visual system. In *The Cognitive Neurosciences*, M.S. Gazzaniga, ed. (Cambridge, MA: MIT Press), pp. 313–326.
- Carandini, M., and Heeger, D.J. (2012). Normalization as a canonical neural computation. *Nat. Rev. Neurosci.* 13, 51–62.
- Cavanaugh, J.R., Bair, W., and Movshon, J.A. (2002a). Nature and interaction of signals from the receptive field center and surround in macaque V1 neurons. *J. Neurophysiol.* 88, 2530–2546.
- Cavanaugh, J.R., Bair, W., and Movshon, J.A. (2002b). Selectivity and spatial distribution of signals from the receptive field surround in macaque V1 neurons. *J. Neurophysiol.* 88, 2547–2556.
- Chagnac-Amitai, Y., and Connors, B.W. (1989). Horizontal spread of synchronized activity in neocortex and its control by GABA-mediated inhibition. *J. Neurophysiol.* 61, 747–758.

- Chauvette, S., Volgushev, M., and Timofeev, I. (2010). Origin of active states in local neocortical networks during slow sleep oscillation. *Cereb. Cortex* 20, 2660–2674.
- Chavane, F., Sharon, D., Jancke, D., Marre, O., Frégnac, Y., and Grinvald, A. (2011). Lateral spread of orientation selectivity in V1 is controlled by intracortical cooperativity. *Front Syst Neurosci.* 5, 4.
- Chen, C.C., Kasamatsu, T., Polat, U., and Norcia, A.M. (2001). Contrast response characteristics of long-range lateral interactions in cat striate cortex. *Neuroreport* 12, 655–661.
- Compte, A., and Wang, X.J. (2006). Tuning curve shift by attention modulation in cortical neurons: a computational study of its mechanisms. *Cereb. Cortex* 16, 761–778.
- Compte, A., Sanchez-Vives, M.V., McCormick, D.A., and Wang, X.J. (2003). Cellular and network mechanisms of slow oscillatory activity (<1 Hz) and wave propagations in a cortical network model. *J. Neurophysiol.* 89, 2707–2725.
- Cowey, A. (1964). Projection of the retina on to striate and prestriate cortex in the squirrel monkey, *Saimiri sciureus*. *J. Neurophysiol.* 27, 366–393.
- Creutzfeldt, O.D., Garey, L.J., Kuroda, R., and Wolff, J.R. (1977). The distribution of degenerating axons after small lesions in the intact and isolated visual cortex of the cat. *Exp. Brain Res.* 27, 419–440.
- Derdikman, D., Hildesheim, R., Ahissar, E., Arieli, A., and Grinvald, A. (2003). Imaging spatiotemporal dynamics of surround inhibition in the barrels somatosensory cortex. *J. Neurosci.* 23, 3100–3105.
- Destexhe, A., and Contreras, D. (2006). Neuronal computations with stochastic network states. *Science* 314, 85–90.
- Ebersole, J.S., and Kaplan, B.J. (1981). Intracortical evoked potentials of cats elicited by punctate visual stimuli in receptive field peripheries. *Brain Res.* 224, 160–164.
- Ermentrout, G.B., and Kleinfeld, D. (2001). Traveling electrical waves in cortex: insights from phase dynamics and speculation on a computational role. *Neuron* 29, 33–44.
- Ferezou, I., Haiss, F., Gentet, L.J., Aronoff, R., Weber, B., and Petersen, C.C. (2007). Spatiotemporal dynamics of cortical sensorimotor integration in behaving mice. *Neuron* 56, 907–923.
- Finn, I.M., Priebe, N.J., and Ferster, D. (2007). The emergence of contrast-invariant orientation tuning in simple cells of cat visual cortex. *Neuron* 54, 137–152.
- Fisken, R.A., Garey, L.J., and Powell, T.P. (1975). The intrinsic, association and commissural connections of area 17 on the visual cortex. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 272, 487–536.
- Fitzpatrick, D. (2000). Seeing beyond the receptive field in primary visual cortex. *Curr. Opin. Neurobiol.* 10, 438–443.
- Freund, T.F., Martin, K.A.C., and Whitteridge, D. (1985). Innervation of cat visual areas 17 and 18 by physiologically identified X- and Y- type thalamic afferents. I. Arborization patterns and quantitative distribution of postsynaptic elements. *J. Comp. Neurol.* 242, 263–274.
- Fukunishi, K., Murai, N., and Uno, H. (1992). Dynamic characteristics of the auditory cortex of guinea pigs observed with multichannel optical recording. *Biol. Cybern.* 67, 501–509.
- Gil, Z., Connors, B.W., and Amitai, Y. (1997). Differential regulation of neocortical synapses by neuromodulators and activity. *Neuron* 19, 679–686.
- Gilbert, C.D. (1992). Horizontal integration and cortical dynamics. *Neuron* 9, 1–13.
- Gilbert, C.D., and Wiesel, T.N. (1979). Morphology and intracortical projections of functionally characterised neurones in the cat visual cortex. *Nature* 280, 120–125.
- Golomb, D., and Amitai, Y. (1997). Propagating neuronal discharges in neocortical slices: computational and experimental study. *J. Neurophysiol.* 78, 1199–1211.
- Grinvald, A., and Hildesheim, R. (2004). VSDI: a new era in functional imaging of cortical dynamics. *Nat. Rev. Neurosci.* 5, 874–885.
- Grinvald, A., Lieke, E.E., Frostig, R.D., and Hildesheim, R. (1994). Cortical point-spread function and long-range lateral interactions revealed by real-time optical imaging of macaque monkey primary visual cortex. *J. Neurosci.* 14, 2545–2568.
- Haider, B., and McCormick, D.A. (2009). Rapid neocortical dynamics: cellular and network mechanisms. *Neuron* 62, 171–189.
- Haider, B., Krause, M.R., Duque, A., Yu, Y., Touryan, J., Mazer, J.A., and McCormick, D.A. (2010). Synaptic and network mechanisms of sparse and reliable visual cortical activity during nonclassical receptive field stimulation. *Neuron* 65, 107–121.
- Harris, K.D., and Thiele, A. (2011). Cortical state and attention. *Nat. Rev. Neurosci.* 12, 509–523.
- Hetherington, P.A., and Swindale, N.V. (1999). Receptive field and orientation scatter studied by tetrode recordings in cat area 17. *Vis. Neurosci.* 16, 637–652.
- Higo, S., Udaka, N., and Tamamaki, N. (2007). Long-range GABAergic projection neurons in the cat neocortex. *J. Comp. Neurol.* 503, 421–431.
- Hirsch, J.A., and Gilbert, C.D. (1991). Synaptic physiology of horizontal connections in the cat's visual cortex. *J. Neurosci.* 11, 1800–1809.
- Huang, X., Xu, W., Liang, J., Takagaki, K., Gao, X., and Wu, J.Y. (2010). Spiral wave dynamics in neocortex. *Neuron* 68, 978–990.
- Hubel, D.H., and Wiesel, T.N. (1959). Receptive fields of single neurones in the cat's striate cortex. *J. Physiol.* 148, 574–591.
- Hubel, D.H., and Wiesel, T.N. (1962). Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J. Physiol.* 160, 106–154.
- Humphrey, A.L., Sur, M., Uhlrich, D.J., and Sherman, S.M. (1985). Projection patterns of individual X- and Y-cell axons from the lateral geniculate nucleus to cortical area 17 in the cat. *J. Comp. Neurol.* 233, 159–189.
- Jancke, D., Chavane, F., Naaman, S., and Grinvald, A. (2004). Imaging cortical correlates of illusion in early visual cortex. *Nature* 428, 423–426.
- Jin, J.Z., Wang, Y., Swadlow, H.A., and Alonso, J.M. (2011). Population receptive fields of ON and OFF thalamic inputs to an orientation column in visual cortex. *Nat. Neurosci.* 14, 232–238.
- Kapadia, M.K., Westheimer, G., and Gilbert, C.D. (1999). Dynamics of spatial summation in primary visual cortex of alert monkeys. *Proc. Natl. Acad. Sci. USA* 96, 12073–12078.
- Kenet, T., Bibitchkov, D., Tsodyks, M., Grinvald, A., and Arieli, A. (2003). Spontaneously emerging cortical representations of visual attributes. *Nature* 425, 954–956.
- Kitano, M., Niiyama, K., Kasamatsu, T., Sutter, E.E., and Norcia, A.M. (1994). Retinotopic and nonretinotopic field potentials in cat visual cortex. *Vis. Neurosci.* 11, 953–977.
- Kohn, A., and Smith, M.A. (2005). Stimulus dependence of neuronal correlation in primary visual cortex of the macaque. *J. Neurosci.* 25, 3661–3673.
- Lauritzen, M. (2001). Cortical spreading depression in migraine. *Cephalalgia* 21, 757–760.
- Lee, S.H., Blake, R., and Heeger, D.J. (2005). Traveling waves of activity in primary visual cortex during binocular rivalry. *Nat. Neurosci.* 8, 22–23.
- London, J.A., Cohen, L.B., and Wu, J.Y. (1989). Optical recordings of the cortical response to whisker stimulation before and after the addition of an epileptogenic agent. *J. Neurosci.* 9, 2182–2190.
- Looger, L.L., and Griesbeck, O. (2012). Genetically encoded neural activity indicators. *Curr. Opin. Neurobiol.* 22, 18–23.
- Matsubara, J.A., and Phillips, D.P. (1988). Intracortical connections and their physiological correlates in the primary auditory cortex (AI) of the cat. *J. Comp. Neurol.* 268, 38–48.

- McDonald, C.T., and Burkhalter, A. (1993). Organization of long-range inhibitory connections with rat visual cortex. *J. Neurosci.* *13*, 768–781.
- Mitzdorf, U. (1985). Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. *Physiol. Rev.* *65*, 37–100.
- Mohajerani, M.H., McVea, D.A., Fingas, M., and Murphy, T.H. (2010). Mirrored bilateral slow-wave cortical activity within local circuits revealed by fast bihemispheric voltage-sensitive dye imaging in anesthetized and awake mice. *J. Neurosci.* *30*, 3745–3751.
- Mountcastle, V.B. (1957). Modality and topographic properties of single neurons of cat's somatic sensory cortex. *J. Neurophysiol.* *20*, 408–434.
- Nauhaus, I., Busse, L., Carandini, M., and Ringach, D.L. (2009). Stimulus contrast modulates functional connectivity in visual cortex. *Nat. Neurosci.* *12*, 70–76.
- Nauhaus, I., Busse, L., Ringach, D.L., and Carandini, M. (2012). Robustness of traveling waves in ongoing activity of visual cortex. *J. Neurosci.* *32*, 3088–3094.
- Nenadic, Z., Ghosh, B.K., and Ulinski, P. (2003). Propagating waves in visual cortex: a large-scale model of turtle visual cortex. *J. Comput. Neurosci.* *14*, 161–184.
- Ohki, K., Chung, S., Ch'ng, Y.H., Kara, P., and Reid, R.C. (2005). Functional imaging with cellular resolution reveals precise micro-architecture in visual cortex. *Nature* *433*, 597–603.
- Ohki, K., Chung, S., Kara, P., Hübener, M., Bonhoeffer, T., and Reid, R.C. (2006). Highly ordered arrangement of single neurons in orientation pinwheels. *Nature* *442*, 925–928.
- Orbach, H.S., Cohen, L.B., and Grinvald, A. (1985). Optical mapping of electrical activity in rat somatosensory and visual cortex. *J. Neurosci.* *5*, 1886–1895.
- Ozeki, H., Finn, I.M., Schaffer, E.S., Miller, K.D., and Ferster, D. (2009). Inhibitory stabilization of the cortical network underlies visual surround suppression. *Neuron* *62*, 578–592.
- Petersen, C.C., and Sakmann, B. (2001). Functionally independent columns of rat somatosensory barrel cortex revealed with voltage-sensitive dye imaging. *J. Neurosci.* *21*, 8435–8446.
- Petersen, C.C., Grinvald, A., and Sakmann, B. (2003a). Spatiotemporal dynamics of sensory responses in layer 2/3 of rat barrel cortex measured in vivo by voltage-sensitive dye imaging combined with whole-cell voltage recordings and neuron reconstructions. *J. Neurosci.* *23*, 1298–1309.
- Petersen, C.C., Hahn, T.T., Mehta, M., Grinvald, A., and Sakmann, B. (2003b). Interaction of sensory responses with spontaneous depolarization in layer 2/3 barrel cortex. *Proc. Natl. Acad. Sci. USA* *100*, 13638–13643.
- Pinto, D.J., Patrick, S.L., Huang, W.C., and Connors, B.W. (2005). Initiation, propagation, and termination of epileptiform activity in rodent neocortex in vitro involve distinct mechanisms. *J. Neurosci.* *25*, 8131–8140.
- Polat, U., Mizobe, K., Pettet, M.W., Kasamatsu, T., and Norcia, A.M. (1998). Collinear stimuli regulate visual responses depending on cell's contrast threshold. *Nature* *391*, 580–584.
- Prechtl, J.C., Bullock, T.H., and Kleinfeld, D. (2000). Direct evidence for local oscillatory current sources and intracortical phase gradients in turtle visual cortex. *Proc. Natl. Acad. Sci. USA* *97*, 877–882.
- Ray, S., and Maunsell, J.H. (2011). Network rhythms influence the relationship between spike-triggered local field potential and functional connectivity. *J. Neurosci.* *31*, 12674–12682.
- Reimer, A., Hubka, P., Engel, A.K., and Kral, A. (2011). Fast propagating waves within the rodent auditory cortex. *Cereb. Cortex* *21*, 166–177.
- Ringach, D.L. (2009). Spontaneous and driven cortical activity: implications for computation. *Curr. Opin. Neurobiol.* *19*, 439–444.
- Rockland, K.S., and Lund, J.S. (1982). Widespread periodic intrinsic connections in the tree shrew visual cortex. *Science* *215*, 1532–1534.
- Roland, P.E., Hanazawa, A., Undeman, C., Eriksson, D., Tompa, T., Nakamura, H., Valentiniene, S., and Ahmed, B. (2006). Cortical feedback depolarization waves: a mechanism of top-down influence on early visual areas. *Proc. Natl. Acad. Sci. USA* *103*, 12586–12591.
- Rubino, D., Robbins, K.A., and Hatsopoulos, N.G. (2006). Propagating waves mediate information transfer in the motor cortex. *Nat. Neurosci.* *9*, 1549–1557.
- Sakata, S., and Harris, K.D. (2009). Laminar structure of spontaneous and sensory-evoked population activity in auditory cortex. *Neuron* *64*, 404–418.
- Sanchez-Vives, M.V., and McCormick, D.A. (2000). Cellular and network mechanisms of rhythmic recurrent activity in neocortex. *Nat. Neurosci.* *3*, 1027–1034.
- Sceniak, M.P., Ringach, D.L., Hawken, M.J., and Shapley, R. (1999). Contrast's effect on spatial summation by macaque V1 neurons. *Nat. Neurosci.* *2*, 733–739.
- Schwartz, O., and Simoncelli, E.P. (2001). Natural signal statistics and sensory gain control. *Nat. Neurosci.* *4*, 819–825.
- Seriès, P., Georges, S., Lorenceau, J., and Frégnac, Y. (2002). Orientation dependent modulation of apparent speed: a model based on the dynamics of feed-forward and horizontal connectivity in V1 cortex. *Vision Res.* *42*, 2781–2797.
- Sharon, D., Jancke, D., Chavane, F., Na'aman, S., and Grinvald, A. (2007). Cortical response field dynamics in cat visual cortex. *Cereb. Cortex* *17*, 2866–2877.
- Silver, M.A., Shenhav, A., and D'Esposito, M. (2008). Cholinergic enhancement reduces spatial spread of visual responses in human early visual cortex. *Neuron* *60*, 904–914.
- Sit, Y.F., Chen, Y., Geisler, W.S., Miikkulainen, R., and Seidemann, E. (2009). Complex dynamics of V1 population responses explained by a simple gain-control model. *Neuron* *64*, 943–956.
- Slovin, H., Arieli, A., Hildesheim, R., and Grinvald, A. (2002). Long-term voltage-sensitive dye imaging reveals cortical dynamics in behaving monkeys. *J. Neurophysiol.* *88*, 3421–3438.
- Song, W.J., Kawaguchi, H., Totoki, S., Inoue, Y., Katura, T., Maeda, S., Inagaki, S., Shirasawa, H., and Nishimura, M. (2006). Cortical intrinsic circuits can support activity propagation through an isofrequency strip of the guinea pig primary auditory cortex. *Cereb. Cortex* *16*, 718–729.
- Steriade, M., Nuñez, A., and Amzica, F. (1993). A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *J. Neurosci.* *13*, 3252–3265.
- Tomioka, R., Okamoto, K., Furuta, T., Fujiyama, F., Iwasato, T., Yanagawa, Y., Obata, K., Kaneko, T., and Tamamaki, N. (2005). Demonstration of long-range GABAergic connections distributed throughout the mouse neocortex. *Eur. J. Neurosci.* *21*, 1587–1600.
- Tsodyks, M., Kenet, T., Grinvald, A., and Arieli, A. (1999). Linking spontaneous activity of single cortical neurons and the underlying functional architecture. *Science* *286*, 1943–1946.
- Tye, K.M., and Deisseroth, K. (2012). Optogenetic investigation of neural circuits underlying brain disease in animal models. *Nat. Rev. Neurosci.* *13*, 251–266.
- Wu, J.Y., Xiaoying Huang, and Chuan Zhang. (2008). Propagating waves of activity in the neocortex: what they are, what they do. *Neuroscientist* *14*, 487–502.
- Xu, W., Huang, X., Takagaki, K., and Wu, J.Y. (2007). Compression and reflection of visually evoked cortical waves. *Neuron* *55*, 119–129.