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Barrels in the Desert: The Sde Boker Workshop on Neocortical Circuits

Meeting Report

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One of great mysteries in biology is the function of the cerebral cortex. The neocortex constitutes the largest part of the brain in mammals and is essential for complex mental functions such as perception, motor planning, memory, imagination, language, attention, and awareness. The anatomical organization of the cerebral cortex has apparently not changed significantly since its evolutionary appearance approximately 300 million years ago (Allman, 1990). Its cellular components and basic circuitry develop in a stereotyped fashion (Miller, 1988; Rakic, 1988) that is conserved across different parts of the cortex and different mammalian species. Results from seminal physiological studies (Hubel and Wiesel, 1977; Mountcastle, 1982), suggesting that the cortex is composed of functional modules, led to the idea that the neocortex may be comprised of many copies of a basic circuit having similar functional characteristics. According to this view, the computation performed by cortical circuits in different cortical regions would be the same, and the apparent functional differences among areas would be due to their different inputs (Hubel and Wiesel, 1974). In spite of substantial progress in the elucidation of the macro- and microanatomy of cortical tissue (Gilbert, 1983; White, 1989; Douglas and Martin, 1990; Braitenberg and Schüzt, 1991) and in the understanding of some receptive field properties of cortical neurons (Hubel, 1996), the nature of the computation carried out by cortical modules is still largely unknown, and a unified theory of cortical function remains elusive (Crick and Asanuma, 1986).

While gaps in our understanding of the cerebral cortex have often been attributed to the extraordinarily large number of cortical neurons, their small size, and the apparent complexity of their connectivity, a recent meeting, "The Sde Boker Workshop in Neocortical Circuits," underscored the challenges of investigating the dynamics of neural circuits whose operations change on timescales ranging from a few milliseconds to the life span of the individual organism. The meeting, organized by Yael Amitai and Michael Gutnick at the Sde Boker campus of Ben Gurion University of the Negev desert of Israel, offered an excellent opportunity to review recent experimental and theoretical advances in cortical research and to put them in a coherent context. The focus of the meeting was the anatomical and functional organization of the rodent somatosensory cortex, also known as the barrel field of mice and rats (Figure 1; Woolsey and Van der Loos, 1970; Jones and Diamond, 1995), although investigators working on other cortices brought a necessary counterpoint and perspective to the topics discussed. We have organized this review of the meeting according to the major themes that emerged from the presentations and discussions, adopting the convention of citing only the individual presenting the work and limiting citations to the essential ones.

Is There a Uniform Design to the Neocortex?

The opening presentation (T. Woolsey, Washington University) underscored two basic themes of the meeting: (1) that commonalties among cortical circuits even in different species are, at this stage of our understanding, more compelling than their differences and (2) that the rodent barrel cortex provides a particularly advantageous model system for elucidating the operations of cortical circuits. As early as the 1920s, long before the advent of transgenic mice, Lorente de Nó chose to base his comprehensive study of the cortical circuitry in an area of the mouse neocortex thought to be auditory cortex, which is now appreciated to be the face region of the somatosensory cortex (Lorente de Nó, 1922). Anatomically, barrels are well-defined structures (100–300 μm in diameter in mice and 150–600 μm diameter in rats) and contain relatively few neurons (in mice, $\sim$1500–2500 neurons per large barrel). Equally important, each barrel is associated with an identified sensory organ, a mystacial vibrissa, that can be manipulated in developmental and sensory physiology experiments. Thus, not only is a detailed description of barrel cortex microcircuitry in principle feasible, but the receptive field properties of its neurons can be increasingly understood on the basis of interconnections within and among the modular units that comprise the whisker representation. In addition, rodents are ideal laboratory animals and have long been favorites for in vitro studies of cortical and hippocampal circuitry. In mice, for instance, it is possible to cut brain slices that include the ventrobasal thalamus, the cortical barrel field, and the intact thalamocortical and corticothalamic pathways (Agmon and Connors, 1991). With the increasing sophistication of in vitro methodologies and the advent of gene-manipulation technologies, which can generate an impressive arsenal of animals with mutations in almost any proteins, the rodent brain is becoming an ever more useful model for studying cortical circuits.

In spite of major similarities among cortical circuits, a significant cautionary note was provided by several presentations describing important regional and/or species-related differences in cortical circuits. For example, subtypes of chandelier cells, identified by their immunoreactivity to parvalbumin and calbindin, exist in the lower layers of human neocortex but are absent in monkeys (J. De Felipe, Cajal Institute). Because individual chandelier cells make many inhibitory synapses on dozens of nearby pyramidal neurons, differences in these neurons may underlie species-specific differences in local circuits. Similarly, synaptic depression appears to be a hallmark of thalamocortical synapses in mouse barrel cortex (Y. Amitai, Ben Gurion University), but not in the cat (M. Steriade, Laval University), suggesting that cortical circuits in different species have evolved somewhat

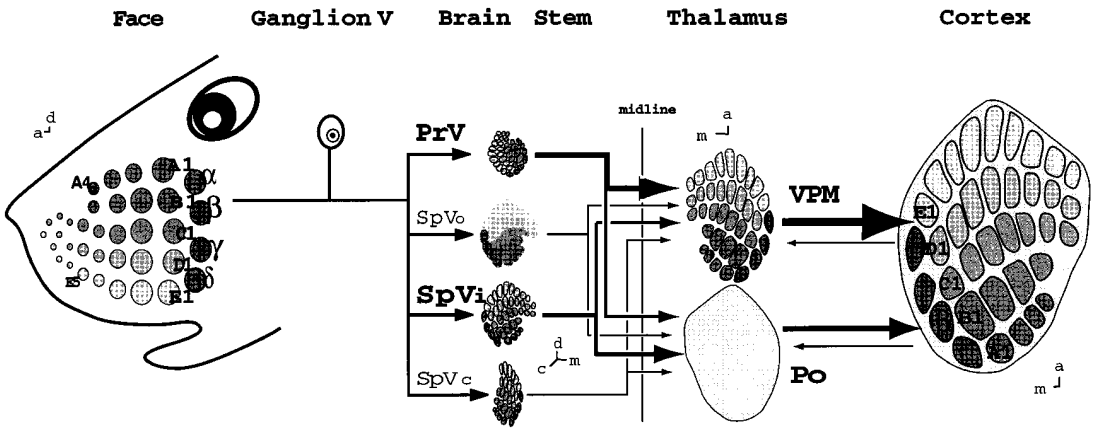

Figure 1. The Vibrissae–Barrel Somatosensory Pathway

Schematic diagram summarizing the major stages of the rodent barrel pathway. Sensory information from the mystacial whiskers of the face sequentially reaches the sensory nuclei of the trigeminus in the brain stem, the thalamus, and the primary somatosensory cortex. Each vibrissa is associated with a brain stem "barrelette" (Ma, 1991), a thalamic "barreloid" (Van der Loos, 1976), and a cortical "barrel" (Woolsey and Van der Loos, 1970). PrV, nucleus principalis of the trigeminus; SpVo, spinal nucleus of the trigeminus pars oralis; SpVi, spinal nucleus of the trigeminus pars interpolaris; SpVc, spinal nucleus of the trigeminus pars caudalis; VPM, ventral posterior medial (ventrobasal) nucleus of the thalamus; and Po, posterior nucleus of the thalamus. (Courtesy of Thomas Woolsey, Washington University).

different mechanisms to regulate circuit excitability. Also, in rats, paired-pulse electrical stimulation of the ventrobasal complex, the major thalamic relay for sensory information, elicits a decrementing local field potential response. However, the same type of stimulation applied to the ventrolateral nucleus, the thalamic 'motor' projection nucleus, evokes an augmenting one, which is abolished when the animal is alert and active (B. Connors, Brown University). Thus, species may differ with respect to the regional organization of thalamocortical pathways, and even in the same animal thalamic afferents can differentially engage local cortical circuits such that the response of the same thalamocortical system may be highly state dependent.

Circuit Models: Distributed Processing of Precise Timing Patterns

A recurring theme of the conference was the "microcircuit credo", i.e., that detailed description of the cortical microcircuit is essential for an eventual understanding of how it "works". A provocative finding from quantitative ultrastructural studies of mouse barrels is that thalamic afferents synapse with any postsynaptic neuronal target (E. White, Ben Gurion University). This includes neighboring spiny and smooth barrel neurons as well as superficial and deep pyramidal cells having dendrites that pass through the same barrel. While this finding might suggest a lack of specificity of the thalamic projection, the relative numbers of thalamic synapses depend on the type of postsynaptic neuron (e.g., spiny versus smooth) and, in the case of neurons having similar gross morphologies (i.e., pyramidal cells), on the projection target of its axon. Thus, although the thalamocortical pathway is highly distributed, there is a quantitative specificity to its projections. Similar rules apply to callosal and perhaps to interlaminar connections.

In mouse barrels, thalamic afferents contribute only ~13% of the asymmetric (excitatory) synapses on spiny stellate cells (White), and estimates in layer 4 of cat visual cortex are as small as 6% (Ahmed et al., 1994). In spite of their small numerical contribution, thalamic afferents adequately drive cortical layer IV neurons in vivo, so much so that early models of visual cortical circuitry proposed that receptive fields of layer IV neurons are largely a reflection of their thalamic inputs (Hubel and Wiesel, 1977). Other models, recognizing the large number of nonthalamic synapses, suppose that intracortical excitatory synapses selectively amplify weak thalamic inputs (Douglas et al., 1989, 1995; Ben-Yishai et al., 1995; Somers et al., 1995). One way to evaluate the contribution of thalamocortical synapses is to silence the local, recurrent cortical connections while monitoring synaptic potentials evoked in individual cortical neurons in response to sensory stimulation. Cooling the cortical tissue in cat visual cortex abolishes action potentials in most cortical layers but does not eliminate thalamocortical excitatory postsynaptic potentials (EPSPs) nor diminish the orientation selectivity of simple cells, determined from the neuron's membrane potential (D. Ferster, Northwestern University). What then does the layer IV circuitry do? An explanation proposed on the basis of in vivo recordings and computer simulations from rat barrel cortex is that the net effect of barrel circuitry is inhibitory. This is consistent with findings that thalamocortical synapses are found on proximal dendrites and somata of inhibitory neurons (White). The suppressive effect of the network is, however, counteracted by local recurrent excitatory circuits; the latter are most strongly engaged by temporally synchronous thalamic inputs, such as those associated with preferred stimuli, e.g., deflections of the barrel's principal whisker (D. Simons, University of Pittsburgh). These damping circuits are therefore sensitive to input timing, not to input magnitude. Thus, rather than creating or enhancing stimulus specificity, local circuits in layer IV may contribute to contrast gain control, e.g., maintaining the orientation tuning inherent in the circuit's feed-forward thalamic inputs over a range of luminance contrasts.

The role of timing in cortical processing was further emphasized by W. Singer (Max Plank Institute for Brain Research, Frankfurt), who argued that cortical neurons are precise and fast. Noting that behavioral responses to texture discriminations and face recognition occur soon after the arrival of visual information in the cortex, he suggested that the most relevant perceptual information is carried by the very first spikes that traverse the cortex following a visual stimulus. In the cat, retinal ganglion cells from different areas of the retina fire within a millisecond of each other when stimulated with a contiguous spot of light. On the other hand, if they are simultaneously stimulated by two spots of light, their spikes become desynchronized. A similar effect is observed in the lateral geniculate nucleus and in primary visual cortex, even among distantly located neurons. Does this synchronization have a role in organizing behavioral responses, or is it an epiphenomenon of the circuitry? Cats with strabismus can be made to alternate their eye dominance by changing the contrast of the visual stimulus to each eye. When an eye becomes dominant, and is therefore used for perceptual decisions by the animal, synchronization among cortical neurons increases. Circuits that operate as coincidence detectors could distribute the information stream rapidly, faithfully, and economically, requiring only a few well-timed spikes.

The importance of spike timing within distributed interconnected circuits was suggested also by in vitro studies involving intracellular recordings from connected pairs of neurons, followed by ultrastructural reconstructions of their synaptic contacts (A. Thomson, Royal Free Hospital; E. Buhl, MRC Neuroanatomical Unit; H. Markram, Weizmann Institute). These results reveal a distributed connectivity in local pyramidal cell circuits. For example, two connected pyramidal neurons have on average 3–10 synaptic contacts (Thomson, Markram), suggesting the absence of anatomically strong "labeled lines" for excitatory connections. From these numbers, it is estimated that each intrinsically bursting (IB) layer V pyramidal neuron contacts 20–50 other nearby IB neurons. The pattern of interconnectivity is probably not random because the number of contacts does not follow a Poisson distribution and the proportion of autapses is higher than that expected by chance. Such small networks of bursting neurons form recurrent microcircuits (Markram) that can generate more widespread synchronized neuronal activity, such as the patterned activity observed during epileptic seizures (Connors, 1984). Interestingly, in the mouse barrel field, tangential brain slices composed almost exclusively of layer IV can still sustain epileptic discharges, suggesting that spiny stellate cells are also synaptically connected among themselves, forming small networks (M. Gutnick, Ben Gurion University).

Neuronal Integration: Temporal and Spatial Summation

As exemplified by many presentations, in vitro methodologies are providing powerful approaches for studying the nature and mechanisms of synaptic integration in cortical microcircuits. Simultaneous intracellular recordings from pairs or triads of connected neurons and optical imaging of individual spines, combined with more traditional pharmacological and pathway stimulation techniques, permit the investigation of cortical synaptic function with unprecedented levels of resolution, illuminating the types of computations that cortical microcircuits are best suited to perform. These results suggest that individual cortical neurons may be exquisitely sensitive to the timing of synaptic inputs distributed over a large spatial extent of individual dendrites. Experiments in vitro, however, explore activation regimes that could differ from those in the awake animal, and synaptic integration needs to be also explored in vivo with approaches like dual intracellular recordings (Steriade) or dendritic imaging (Svoboda et al., 1997).

Temporal summation among excitatory neurons appears to be dominated by short-term depression. In rat cortex, synapses between certain types of pyramidal neurons, studied with paired intracellular recordings, readily depress when stimulated at frequencies higher than 5 Hz (Thomson; Markram). Given the high rates of firing of cortical neurons in vivo, it is expected that under physiological conditions, a large number of synapses will be depressed at any given time, underscoring the importance of distributed synaptic networks. Although synaptic facilitation can occur in horizontal cortico–cortical connections in mouse barrel cortex, thalamocortical synapses impinging on the same postsynaptic target show a strong depression, indicating that the same neuron can sustain different synaptic learning rules for specific inputs (Amitai). In fact, these two classes of synapses have qualitatively different sensitivities to baclofen and to cholinergic neuromodulators such as muscarine and nicotine. Thus, the relative contributions of afferent versus intrinsic synapses may differ depending on the behavioral state of the organism, contributing, for example, to the qualitatively different augmenting and depressing responses evoked by paired stimuli of different thalamic pathways (Connors).

Little is known about mechanisms of spatial summation and coincidence detection in cortical neurons. While EPSP amplification may occur by activation of N-methyl-D-aspartic acid (NMDA) receptors (Thomson), it is unclear whether the specific location of the EPSPs in the dendritic tree influences their interaction. In cultured hippocampal neurons with pyramidal morphologies, spatial summation is linear and independent of the position of the excitatory inputs (Yuste). This implies that the branching pattern of the dendritic tree may not play a major role in integration of excitatory inputs. The linear summation in cultured neurons arises from the balanced action of NMDA receptors, which amplify EPSPs, and I_A potassium channels, which diminish the joint effect of simultaneous EPSPs. Thus, active conductances in dendrites may actually ensure linear summation.

Dendritic conductances can produce sodium or calcium action potentials. In olfactory mitral cells, calcium spikes dominate dendritic excitability (A. Keller, University of Maryland). In pyramidal neurons, sodium spikes are generated in the soma and "back propagate" through the dendritic tree (Stuart and Sakmann, 1994). Simulation studies of excitable dendrites suggest that back-propagating spikes reset the activation state of dendritic channels, which improves the reliability of their

behavior because it accumulates channels in a particular state and makes their behavior as a group less stochastic (I. Segev, Hebrew University). Thus, neurons may be more reliable than the behavior of their conductances would suggest.

Intrinsic and Circuit Oscillations

Cortical neurons have multiple intrinsic cellular mechanisms that can sustain oscillatory responses and may be involved in synchronizing spike firing. CA1 pyramidal neurons have an intrinsic ability to generate bursts of action potentials that can contribute to the excitability of the circuit during an epileptic seizure. The depolarizing envelope that triggers these bursts of action potentials is mediated by a persistent sodium current and terminated by a voltage-gated potassium current (Y. Yaari, Hebrew University). In rat sensorimotor or frontal cortex, subthreshold oscillations can be generated by different mechanisms: at hyperpolarized membrane potentials, 2–5 Hz oscillations are mediated by I_H currents, while at more depolarized potentials, higher frequency oscillations are maintained by a slowly inactivating potassium channel (B. Hutcheon, University of British Columbia and Y. Yarom, Hebrew University). Finally, in rat motor cortex, a rebound excitation produced by the removal of inactivation of T-type calcium channels produces a low-threshold calcium spike that contributes to a short oscillatory response (Connors).

Oscillatory responses in vivo may be important for encoding sensory stimuli and for regulating states of arousal that provide internal contexts for their interpretation. During visual stimulation, 70–100 Hz oscillations occur in cat retina and lateral geniculate nucleus, while in visual cortex, oscillations in the gamma range (30–60 Hz) are prevalent (Singer). The latter can be enhanced with electrical stimulation of the mesencephalic reticular formation, which increases the animal's level of arousal. In cat parietotemporal cortex, intracortical and thalamocortical oscillations dominate the temporal dynamics of the neuronal responses (Steriade). While fast oscillations (20–50 Hz) appear during waking state and rapid eye movement sleep, oscillations $<$15 Hz are characteristic of slow-wave sleep (Steriade et al., 1996). Synchronization of thalamic activity appears to depend on corticothalamic input, which constitutes a large component of cortical outflow. Corticofugal projections to sensory relay nuclei may similarly be involved in the synchronization of activity observed throughout the entire whisker–barrel pathway in awake behaving rats (Nicolelis, Duke University). Oscillations of $\sim$8 Hz precede the onset of whisking and appear first in the cortex, suggesting that activity originating in the cortex is propagated widely throughout a distributed sensorimotor representation of the vibrissae.

How can precise synchronization be achieved among distant populations of neurons with a sparse connectivity? One possible mechanism would be to phase lock oscillations of the spike trains produced by distant neurons (Singer). It is not clear how an oscillation can be synchronized over a wide network of neurons that are connected through series of synapses, which have built-in conduction and synaptic delays. In computer simulations of propagating neuronal discharges in cortical slices lacking GABAergic inhibition, the transient synchrony between neurons does not depend on the distance between them or on monosynaptic connectivity, but rather on the density of excitatory synaptic inputs to individual neurons, which can be as low as 30–100, and on the dynamical properties of the excitatory synapses. During persistent activity, however, excitatory networks with even modest sparseness levels exhibit asynchronous behavior. (D. Golomb, Ben Gurion University).

Inhibitory Control of Cortical Circuits

Excitatory cells, consisting of both local and projection neurons, make up the majority of cortical neurons and form a skeleton of the cortical circuit (Braitenberg and Schüzt, 1991). Nevertheless, the smaller population of inhibitory cells, the vast majority of which are interneurons, profoundly affect overall cortical excitability as well as the specific functions of microcircuits. Anatomically, there is a wide variety of inhibitory interneurons (Buhl, De Felipe). A given class of inhibitory neurons contacts a variety of cells types (divergence), and a given cortical neuron can receive synaptic inputs from several different types of interneurons (convergence). Each class of inhibitory neurons appears to make characteristic patterns of synaptic contacts onto different types of target cells (Buhl), a situation reminiscent of the synaptic relations displayed by thalamocortical and other extrinsic afferents (White). Taken together, these findings indicate that the basic microcircuits of the neocortex are comprised of interconnected excitatory and inhibitory neurons (Thomson, Buhl), many of which also receive monosynaptic inputs from extrinsic sources. Stimulation of mice somatosensory thalamocortical afferents fire inhibitory neurons before the excitatory neurons are sufficiently depolarized to reach threshold (Amitai). A similar fast activation of inhibitory interneurons has been observed in the hippocampus (Miles, 1990). Thus, the effects of thalamic and perhaps other extrinsic inputs to the cortex should be considered as a combination of both feed-forward and recurrent EPSPs and inhibitory postsynaptic potentials. A tight coupling between excitation and inhibition, even in some pathological states, is suggested by findings in post-traumatic models of epileptogenesis in rat cortex where increased excitability is associated with a (seemingly) paradoxical increase in inhibitory postsynaptic potentials (K. Jacobs, Stanford University).

Interestingly, many but not all excitatory synapses on inhibitory neurons facilitate with increasing stimulation frequency (Thomson; Buhl), even though the synapses made by the same neuron on other excitatory neurons depress. This shows that the same axon can form synaptic terminals with very different functional properties, depending on the target neuron (Thomson; Markram). With repetitive stimulation, excitatory neurons also display a slow sodium channel inactivation (I. Fleidervish, Ben Gurion University). Thus, the excitability of an individual neuron within a microcircuit is strongly determined by its immediate preceding synaptic and spiking activity. This could serve to fractionate functionally large

populations of linked excitatory neurons into smaller subnetworks. Cortical dynamics are also strongly influenced by inhibition over longer timescales. Clipping all but two mystacial whiskers causes several days of sensory deprivation and produces a "filling in" of cortical territory of the clipped whiskers by the intact ones (Diamond, University of Trieste). The mechanism underlying this plasticity is thought to involve disinhibition-induced unmasking and subsequent strengthening of weak or latent excitatory connections between barrel columns.

Barrel Development: NMDA and Depolarizing GABA

The advantages of using the rodent barrel field as an experimental model are particularly evident in developmental studies. Like the visual cortex of cats and monkeys (Wiesel, 1982), the development of barrel cortex undergoes a critical period that appears to depend on both activity-dependent and -independent processes (Jones and Diamond, 1995; Killackey et al., 1995). The development of synaptic populations in murine barrel is being characterized quantitatively using thin-section electron microscopy (White). These studies reveal that, although both asymmetric and symmetric synapses increase monotonically during the first few postnatal days, there is a dramatic increase in their numbers beginning at 9 days, corresponding to the period when the animals first begin to make normal patterns of whisking. Interestingly, the sharp increase in inhibitory synapses follows the rise in asymmetric synapses by 1 day. Early thalamocortical synapses are glutaminergic and are dominated by NMDA receptors (R. Malenka, University of California, San Francisco). Because of the relative absence of AMPA receptors, these young synapses are initially silent. Long-term potentiation can be elicited in neonatal thalamocortical slices, but only until about day 9, a time frame corresponding to a critical period during which barrel formation can be affected by damage to the whisker nerves (Malenka; Van der Loos and Woolsey, 1973). It was proposed that the loss of the ability to induce long-term potentiation in thalamocortical synapses and the end of the critical period for barrel development are due to the increasing numbers of functional AMPA receptors ("ampafication") at these synapses.

Horizontal cortico–cortical connections in the barrelfield also have a critical period of development which may be regulated by neuronal activity. Transection of the infraorbital nerve dramatically reduces the level of activity in the barrelfield and leads to an arrested development of the supragranular axonal projections that link neighboring barrel columns. The effect can also be produced by chronic blockade of cortical NMDA receptors (Woolsey). The findings are similar to results from kitten visual cortex, where ocular dominance development can be arrested by NMDA antagonists. Ocular dominance development may also depend on long-term depression, suggesting that activity-dependent synapse modification is bidirectional (Singer; M. Bear, Brown University).

The preponderance of NMDA receptors in developing thalamocortical systems raises the question of how the postsynaptic neurons become depolarized, a function which in adults is mediated by AMPA receptors. One possible solution to this paradox may lie in the depolarizing action of GABA. As in developing hippocampus (Ben-Ari et al., 1989; Cherubini et al., 1991; Hanse et al., 1997), GABA exerts an excitatory effect in the neonatal barrel cortex (Yuste and Katz, 1991), most likely due to a depolarized equilibrium potential for chloride (LoTurco et al., 1995). In fact, depolarizing disynaptic GABA responses are triggered in neonatal barrel cortex after thalamic stimulation (A. Agmon, University of West Virginia). The depolarization appears sufficient to relieve the magnesium blockade of NMDA receptors in the absence of AMPA receptors. Alternatively, a class of voltage-insensitive NMDA receptors could provide a means for activating "silent" NMDA synapses.

Synaptic Plasticity and Learning Rules

Many studies of synaptic plasticity in barrel cortex have employed the paradigms of long-term potentiation and depression. As in hippocampus, results are consistent with a Hebbian-type learning rule wherein coincident activation of pre- and postsynaptic neurons leads to an increase in synaptic strength (Bear; Malenka). Also like hippocampal neurons, a cortical cell can display a decrease in synaptic efficacy if it is activated in the absence of presynaptic activity (Bear; Malenka). This bidirectional effect, predicted by the BCM theory (Bienenstock et al., 1982), is present in the visual cortex of kittens and may contribute to ocular dominance plasticity (Bear). In mice, chronic whisker plucking leads to morphologic alterations in spine heads postsynaptic to thalamocortical afferents, indicating that, under some conditions, activity-dependent alterations in synaptic function can have clear structural counterparts (G. Ben-Shalom, Ben Gurion University).

Examples of both types of synaptic changes can be observed in synaptically connected layer V neurons from rats (Markram). When back-propagating action potentials in the postsynaptic cell coincide with EPSPs triggered by the firing of presynaptic neurons, long-term potentiation occurs. If the back-propagating spikes arrive in the dendrite before the EPSPs, however, long-term depression results. The mechanism underlying these effects is thought to be the influx of calcium into spines, with lower accumulations producing synaptic depression and higher accumulations mediating potentiation (Lisman, 1989). In agreement with this, high, supralinear calcium accumulations can be measured in spines of CA1 neurons when back-propagating spikes and EPSPs coincide (Yuste, Columbia University). The supralinear influxes are specific to the spines receiving the EPSPs and may constitute a form of chemical computation of the temporal coincidence of the input and output of the cell. Changes in calcium, triggered by release from intracellular stores, may mediate other forms of long-term plasticity, such as the muscarinic potentiation of EPSPs in CA1 neurons (M. Segal, Weizmann Institute).

These experiments suggest an important role for back-propagating spikes in short-term synaptic changes. The back-propagating spike, which is sodium dependent, is itself regulated by activity because the occurrence of a

back-propagating spike can limit the effect of subsequent ones (Spruston et al., 1995). While the mechanisms behind this regulation remain unclear, the propagation of dendritic spikes may be influenced by a slow form of inactivation of dendritic sodium channels and by the phosphorylation of sodium channels by protein kinase C (Fleidervish).

Besides long-term potentiation and depression, other forms of synaptic plasticity are likely to be important for regulating cortical activity on a shorter timescale. As mentioned above, synaptic depression appears quite widespread in synapses among excitatory neurons in the cortex (Thomson; Markram), while synaptic facilitation dominates connections between pyramidal neurons and interneurons (Buhl; Thomson). Deciding which of the many different forms of synaptic plasticity is functionally more relevant may require experiments in vivo, which have been carried out in a few cases. As discussed above, augmentation or depression can be demonstrated in vivo in thalamocortical pathways in rats or cats (Connors; Steriade), while cortical disinhibition may mediate whisker pairing in rats (Diamond). In cat primary visual cortex in vivo, contrast adaptation produces a hyperpolarization of adapted neurons that can last for several minutes (Ferster). Finally, olfactory training in rats results in generalized increased excitability and changes in short-term plasticity in the olfactory cortical neurons (Y. Grossman and E. Barkai, Ben Gurion University).

Conclusion: Is the Cortex a Timing Network?

This brief review barely captures the richness and creativity of the ideas presented at the Sde Boker workshop. A common and perhaps unanticipated theme of many presentations was the importance of spike timing in the operations of cortical microcircuits and in their longer-range linkages with other cortical and subcortical networks. Issues like the role of individual spikes and of particular temporal firing patterns, the synchronization of neurons, intrinsic or network oscillations, coincidence detection by networks, individual cells or even individual dendritic spines were preeminent in most presentations and discussions. Thus, the cortex could be viewed as a sophisticated network, which, like an orchestra, interprets particular timing relations, and where every spike counts. Such an assertion would probably have been greeted with considerable skepticism even in the recent past. As the conference indicated, however, a view of the cerebral cortex as a spatially distributed timing network is likely to provide a conceptual framework for exciting new discoveries during the next few years. Certainly, one of the truly exciting outcomes of the workshop was the seamless integration of concepts derived from studies employing approaches as diverse as whole animal physiology, brain slices, cell cultures, or computer simulations. Indeed, it appears that, rather than creating fracture lines around narrow, methodologically based boundaries, the availability of an expanding array of increasingly sophisticated experimental techniques is cross-fertilizing a discipline that is becoming as dynamic as the cortical tissue it seeks to understand.

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