NEURONAL SPECIFICITY & PLASTICITY: FROM SPERRY TO THE BLUE BRAIN

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Abstract

This is a modest review of a couple of papers devoted to an examination of neural specificity and invariance among microcircuits in neocortical columns and minicolums, and the loci of experience dependent plasticity and learning within and between these microcircuits. It focuses on somatosensory cortex, but the appendix covers visual research as well on some of the early work on these issues, from Stratton, to Sperry, Hebb, Mountcastle, Hubel and Wiesel, and T. A. Woolsey and Van der Loos. It starts with a paper from Markram's group on the invariant properties of the microcircuits, and conjectures on a segue form Hebb to Edleman's Darwinian brain theories. Next I review Petersen's paper on neurophysiological studies of experience dependent plasticity in these systems. Some network theory has proved essential to research in these areas, as well as some nifty technical advances in neurophysiological stimulation and recording.

Blue Brain Project

Rosen Industries created the prototype for the Blue Brain. The report is in *Do Androids Dream of Electric Sheep*, which obviously inspired Markram's ***Blue Brain Project*** in Lausanne to reverse-engineer the mammalian brain, creating a complete virtual brain within IBM's BlueGene/L supercomputer. The Blue Brain project proposes a fantastic voyage.[2] The first phase of this project succeeded in simulating a rat cortical column. It claims to use more realistic models of neurons than most neural net models.[3] It has spawned several ancillary projects around the globe, such as the ***Cajal Blue Brain*** in Madrid.

Some of these have included wet biology with the developing brain. One recently received some press (Markram, 2011). It involved neuronal specificity of development in clusters of 40-50 neurons within the cerebral cortex. Here follows a synopsis of their research paper (Perin, Berger, & Markram, 2011).

The paper opens with a critical review of Hebbian and post-Hebbian theory and research. which focuses on (1) changes in synaptic efficiency with use—the *Neurophsiological Postulate*, (2) assemblies of neurons into circuits using those synapses—the *Cell Assembly*, and (3) linkaging and sequencing among these assemblies leading to their conscription into cognitive and learned behavior—the *Phase Sequence*. (Hebb, 1949).

[See appendix 1C infra.]

Next it reviews some research plasticity in neocortical microcircuits, mainly among layer V (L5) pyramidal cells. For neurons within 50µm of each other, every axon terminates on dendrites of all its neighbors (Kalisman. Silverberg, & Markram, 2005) whose plasticity "offers enormous opportunities for functional rewiring of neuron connectivities without major growth and reorganization of their

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[2] With these literary references, I do not mean to belittle this inevitable attempt to push artificial intelligence horizons toward their legitimate but possibly unattainable limits, but once a court jester, always a court jester
[3] Other recent work has demonstrated simulations based on rather realistic models of neurons, e.g., Koene *et al*., 2009.

neural arbors" (p. 1). There is lot of evidence supporting this contention, using single cell electrophysiology (Cheklovskii, 2004; Cheklovskii, Mel, & Slaboda, 2004; Le Be & Markram, 2006; Markram & Tsodyks, 1996; Strepanyants & Chklovskii, 2005). These dimensions are in the ballpark for minicolumn diameters.

[See Appendices 1D (Mountcastle), 1E (Hubel & Wiesel), and especially 1F (Woolsey & Van der Loos), for history of nature of columns and minicolums]

The specific purpose of the research was to explore if microcircuits develop non-randomly or randomly as in Erdös-Renyi networks in early postnatal development, and could, within-minicolumn synaptic plasticity, enable these microcircuits to serve as components in larger plastic circuitry. Does plasticity "operate under constraints of some prescribed synaptic organization."? (pp. 1-2.)

Their research used a standard preparation, a cell population used in neuroscience research on experience-dependent plasticity, namely, L5 pyramidal cells ('thick-tufted subcortically projecting' for them) in the somatosensory cortex of Wistar rats, using *in vitro* living brain slices taken from the developing brain (14^{th}-16^{th} postnatal days). They recorded up to 12 cells at a time with patch-clamp single cell recordings. Connectivity among the neurons was determined by stimulating each cell while recording excitatory post-synaptic potentials (EPSPs)[4] from the others. Pairwise connectivity was proportional to the intersomatic distance, falling off more rapidly with unidirectional connectivity than with bidirectional connectivity, and bidirectional connections were more than twice as frequent as unidirectional connections, i.e., above Monte Carlo expectations.

[For Perin *et al.*'s Figure 1, go to Appendix 2C]

When they compared clusters of 3-8 cells, they observed connectivity that did not exceed expected values based on Monte-Carlo simulations. However, selected patterns of connectivity of 3 and 4 neurons did appear above chance within clusters of 6-8 neurons. "This result could be expected if the smaller motifs . . . are not elementary units in their own right but parts of larger assemblies." (p. 2.) Testing for network properties showed no evidence of a lattice or of hubs characteristic of scale-free networks (on basic properties of networks, see: Abraham, 2011; Barbassi, 1999; Sporns, 2011; Stam & Reijneveld, 2007).

Surprisingly, in 6-cell assemblies embracing greater intersomatic distances, connectivity was not a decreasing, but rather in increasing function of intersomatic distances as was the case with cells considered pairwise. That is, connectivity was a $\cap$-shaped function of intersomatic distances, maximizing in the 100-125 µm range, which means the assemblies might not necessarily be confined within the minicolumns which are in the 30-50 µm range. Furthermore, connection probabilities between two neighbors increased with the number of other common neighbors.

> *"This common neighbor rule is reminiscent of the mutual acquaintance rule of social networks (Jin, Girvan, & Newman, 2001) but without the typical hub-like arrangement. Interestingly, two neurons were more likely to be connected when they both received input from the same common neighbor rather than projecting to a common neighbor, alluding to an even more refined rule relating connection probabilities and types of common neighbors in these directed networks. . . This constraint suggests that experience cannot arbitrarily mold the network topology of cell assemblies." (p.2).*

[For Perin *et al.*'s Figures 3 & S4, go to Appendix 2C]

[4] EPSPs are graded potentials in the dendrites and soma of the receiving neuron, and may or may not result in triggering an action potential (spike) in the receptive neuron.

I think that by 'constraint on network topology' they emphasize the structural nature of the microcircuits as not precluding synaptic change and thus network functioning. They continue to examine connections between these cells, recording from six cells at a time, I suspect to meet the demands of the lower boundaries of the *friendship theorem* of Erdös, Rényi, & Sós, also known as the *theorem on friends and strangers*, as given in *Ramsey's theorem* (Bogomolny, 1996-2011).[5] EPSPs were greater the more connections within the group of cells

[Perin's Figure 6, Appendix 2C]

Perin *et al*. conclude that these constraints suggest less plasticity within these microcircuits support Edelman's theories that

> *"functional neural circuitry arises by selection among neuronal groups that already emerged during embryonic development independent of experience . . . [and that] subsequent experience selects neuronal groups to form secondary repertoires that have survival value (Edelman, 1987, 1993).*
>
> *" The elementary assemblies that we found are interconnected by fewer and weaker strands of connections than within assemblies, which are more amenable to experience-dependent modification (van Rossum et al., 2000). This suggests that experience could uniquely mold overall neuronal circuitry by differently combining elementary assemblies into unique superassemblies or secondary repertoires." (p. 5.)*

Their evidence is largely statistical and structural, and does not involve active investigation of experience-dependent modification of circuits, so I also choose to readact an excellent review paper by Petersen examining such research (Petersen, 2007), which moves us up to layer IV (L4)of the barrel cortex and the research subsequent to that of Woolsey & Van de Loos (1970; see Appendix 1F).

Roll out the Barrel

Rats, mice, and other rodents are nocturnal, so they have not developed the complex visual processing capabilities of primates, cats, and many other animals, such as found in the studies by Hubel and Wiesel. But evolution has favored them with a similarly complex ability to analyze 3D properties, including integrating bilateral sensory information, with their whiskers. The neocortical terminus of much of this information is in minicolumns, especially in, but not confined to, L4 pyramidal cells, an area frequently referred to as 'barrels'.
(Figure from Göttinger Barrel Group, http://neuro.ukat.gwdg.de/barrels/)

Petersen's overview of the system, Figure 1, is supplemented by Appendix 1F and Simon's photomicrograph of the correspondence of the map of the whiskers to the map of the somatosensory cortex as in Petersen's Figure 1, below.

[5] The *friendship theorem* states that in a group of six people, at least three of them (pair-wise) are mutual acquaintances or there are at least three are mutual strangers. It is usually depicted by a two color graph as in the present paper where the nodes are neurons instead of people, and it has been shown that there are at least two monochromatic triangles. Generalizations of the theorem have a lower bound to the number of nodes for which the theorem holds, namely six, stated in Ramsey's theorem. (See Bogomolny or Wikipedia.)

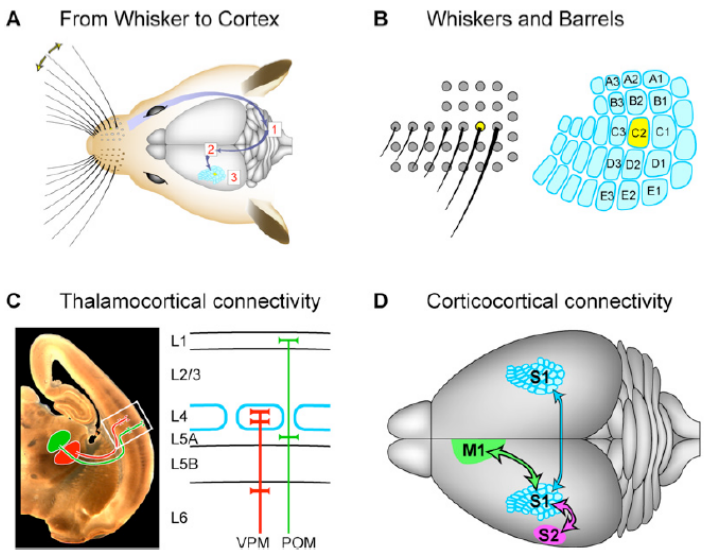


Figure 1. Synaptic Pathways for Processing Whisker-Related Sensory Information in the Rodent Barrel Cortex

(A) Deflection of a whisker evokes action potentials in sensory neurons of the trigeminal nerve, which release glutamate at a first synapse in the brain stem (1). The brain stem neurons send sensory information to the thalamus (2), where a second glutamatergic synapse excites thalamocortical neurons projecting to the primary somatosensory barrel cortex (3).

(B) The layout of whisker follicles (left, only C-row whiskers shown) on the snout of the rodent is highly conserved and is identical between rats and mice. There are obvious anatomical structures termed "barrels" in layer 4 of the primary somatosensory neocortex (right), which are laid out in a near identical pattern to the whiskers. The standard nomenclature for both whiskers and barrels consists of the rows A–E and the arcs 1, 2, 3, etc. The C2 whisker follicle and the C2 barrel are highlighted in yellow.

(C) There are at least two important parallel thalamocortical pathways for signaling whisker-related sensory information to the barrel cortex. Neurons in the ventral posterior medial (VPM) nucleus (labeled red, left) are glutamatergic and signal information relating primarily to deflections of a single whisker. The axons of VPM neurons terminate predominantly in individual layer 4 barrels, with a minor innervation in upper layer 6 (right). Corticothalamic layer 6 neurons provide reciprocal feedback to the VPM (not shown). Neurons of the posterior medial (POM) thalamic nucleus (labeled green, left) have broader receptive fields and are tightly regulated by state-dependent control imposed by zona incerta and the cortex. The axons of POM neurons avoid the layer 4 barrels and target primarily layer 1 and 5A (right). Corticothalamic neurons in layer 5 provide a strong input to POM (not shown).

(D) Neurons in the barrel cortex are reciprocally connected to other cortical areas through long-range glutamatergic corticocortical synapses. The most important pathways connect the primary somatosensory (S1) barrel cortex with secondary somatosensory cortex (S2) and primary motor cortex (M1) on the same hemisphere. Callosal projections are also present but less prominent.

(A) is modified and reproduced from *Neuron*, Knott et al. (2002), Copyright (2002), with kind permission from Cell Press, Elsevier.

From Petersen, 2007. Overview of the mystacial somatosensory system in the rat.

Petersen summarizes the basic nature of the system that makes it ideal system to study dynamical function and plasticity:

> *"This barrel map is in large part genetically specified and forms early in development. Within a few days of birth, the map is fixed, so that even dramatic interventions such as peripheral lesions have little effect upon the somatotopic layout of the barrels. The functional organization, postnatal development, and experience-dependent plasticity of the primary somatosensory whisker cortex can therefore be examined in the context of an invariant anatomical somatotopic map. In addition to long-term plasticity, it is also becoming increasingly clear that the functional operation of cortical circuits in behaving animals is under rapid and strong top-down control, generating highly flexible adaptive sensory processing within the same hard-wired neuronal networks (Gilbert and Sigman, 2007). It is therefore of great importance to examine the dynamic function of the barrel cortex in the context of specific whisker-related behaviors." (p. 339)*

There are several typical cell types found in the barrel that participate in these circuits within and between barrels and other parts of the brain. Here are a few studied by Sun *et al*. (2006) in showing that fast spiking interneurons mediated thalamocortical inhibitory sculpting of the excitatory thalamocortical inputs to the spiny stellate and pyramidal cells. Their Figure 1 follows:

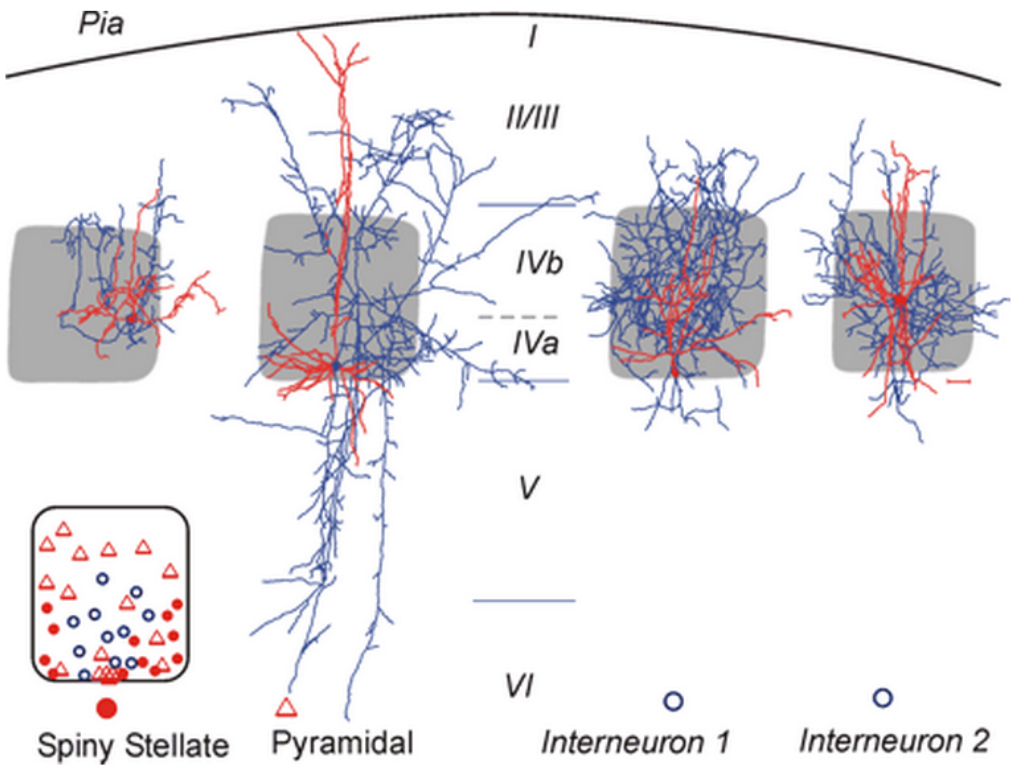
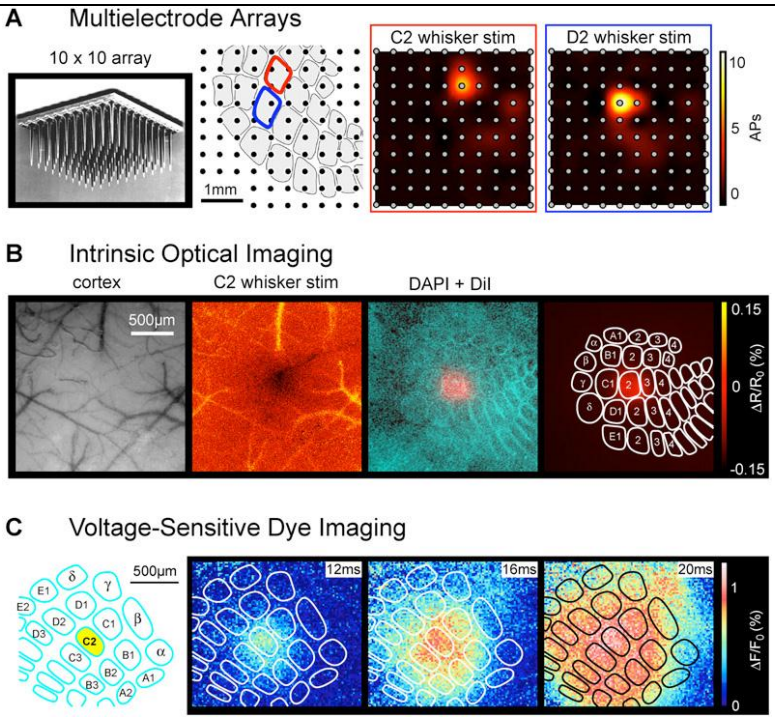


Figure 1. Camera lucida reconstruction of four types of neurons included in this study. Red, Dendrites and somata; blue, axons; gray shading, barrel structure. Scale bar near interneuron 2, 100 μm for all panels. Bottom left inset shows localization of cell bodies within barrel structures: spiny stellate cells (filled red circles), star pyramidal neurons (red open triangles), and basket cells (open blue circles). I–VI, Cortical laminae. Pial surface, Curved line at top of figure.

From Sun *et al.*'s (2006) study of inhibitory and excitatory activity in barrel circuits involved in vibrissal sensation. Note that the spiny stellate cells and interneurons are more confined to the barrels than the axons (blue) of the pyramidal cells. [see **Appendix 2A** for more cortical cell images.]

As with most sensory systems, there are nonspecific extralemniscal reticular ascending pathways as well as specific thalamic lemnicsal pathways of ascending complexity, that terminate mostly on cells in their appropriate primary sensory cortical areas where there is greater variability due to interactions within ongoing activity in the cortex compared to processing earlier in the pathway. Receptive fields are also greater cortically, which "suggest that a primary function of the neocortex is to generate associations of different sensory inputs which are processed in a highly context-dependent manner." (Petersen, p. 340). The POM pathway (green in Peteresen's Figure 1) he refers to as 'paralemniscal' and suggests it has a role in exploration and sensory-motor coordination rather than specific sensory processing.

Since the time of Mountcastle's and Hubel & Wiesel's painstaking extracellular single cell research (Appendices 1 D&E), new technologies have speeded up such research and offer greater temporal and spatial resolution. These include multiple electrode arrays, optical imaging (BOLD and fMRI noninvasive blood oxygen sensing), and the more invasive but more precise voltage-sensitive dye (VSD) imaging.



Petersen's Figure 2 of Mapping in Barrel Cortex

Extracellular Array of 100 electrodes showing responses to deflections two whiskers (rat).
Optical imaging with fluorescent dyes taken through mouse skull; last slide on right shows in vitro confirmation of barrel locus using dye DiI applied to skull, and DAPI after in subsequent slice taken from brain.
VSD of changes of subthreshold membrane voltages and their diffusion from 12 to 20 ms after stimulation.

A is modified from Harris *et al*. (1999). C is modified from Ferezou *et al*. (2006).

The diffusion of the result of postsynaptic subthreshold depolarization outward from the C2 barrel for the deflected C2 whisker of Petersen's Figure 2 is of special interest, not only for its suggestion for the integration of transcortical sensory processes and the possible involvement in cognitive function (integration of cross modality and sensory motor action; perception, learning, etc.), but also for the importance of subthreshold activity in brain function. Petersen points out that such activity dominates as more important than action potentials in this area. It recalls the debates of the 1960s over the relative primacy of unit versus volume-conducted brain activity. Abraham *et al*. (1973) conjectured that waves (as seen by macroelectrode-recorded EEG) might temporally sharpen the sensitivity to transmitted impulses from a study of the recovery of function within cat hypothalamus.

Mountcastle, and Woolsey & Loos inaugurated the investigation of the segregation of specific parameters of stimulation for receptive fields in somatosensory cortex, and Hubel & Wiesel did the same for visual cortex (Appendices 1 D-F) using extracellular microelectrodes. Greater detail of membrane voltage potentials requires intracellular recording which is difficult for network analysis (despite the 12-electrode virtuosity by Perin *et al*. reported above), but the calcium influx initiating the EPSPs that trigger action potentials are now used to study network activity in vivo using calcium sensitive dyes and two-photon microscopy. Stosiek *et al*. (2003) pioneered this technique with cells in layer 2/3.[6] As of the material reviewed here, the discreetness of barrel minicolumns was not

[6] The nature of minicolumns and their involvement in neural plasticity is reviewed in Appendix 1F, especially references to work by Andermann *et al*., Cheetham *et al*., Bruno *et al*., Feldman & Brecht, Simons, and

precise, but was evident more from the fact that directional deflection of a whisker (D3) toward whisker (D2) resulted in activation of neurons within the D3 barrel closer to the D2 barrel (Andermann & Moore, 2006).

[For a review of minicolumns, see Appendix 1F again]

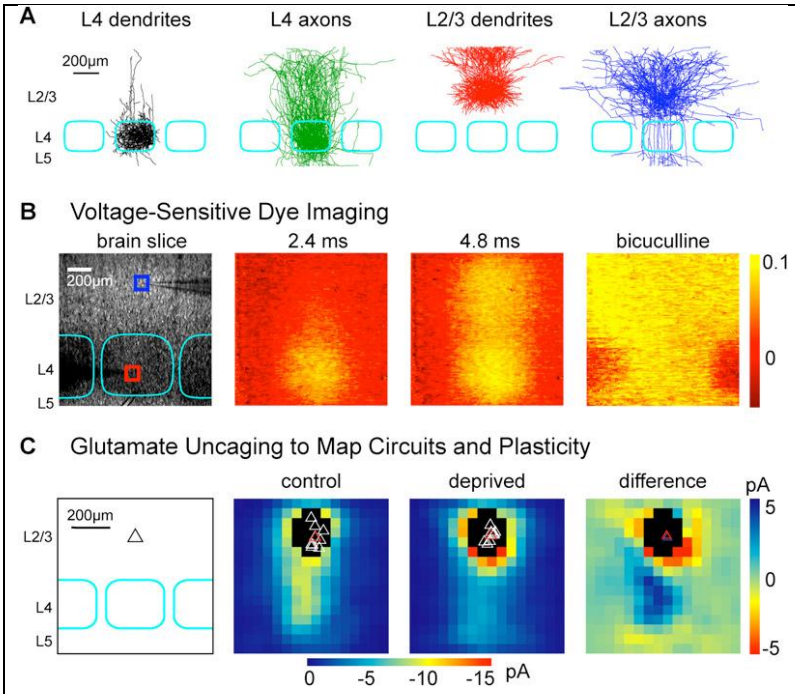


Figure 4 (Petersen, 2007). Simple sensory response pathway in barrel. Excitatory neurons. Dendrites of glutamatergic stellate and pyramidal neurons (black), their axonal projections to L2/3, restricted to barrel column width (green) defining the cortical column, whose dendrites (red) are likewise restricted to the column, but whose axons (blue) extend horizontally beyond the barrel width. VSD shows response to stimulation of L4 spreading to L2/3 at 4.8 ms within the column, but the removal of lateral GABAergic inhibiton

Before whisker removal individul L2/3 neurons respond to L4 stimulation by glutamate uncaging[7], showing confinement to the barrel column. The barel contibutes less with the sensory deprivation.

A and B are modified from Petersen & Sakmann (2001), C is modified from Sheperd *et al*. (2003).

L2/3 neurons thus connect horizontally in barrel cortex beyond the barrel column, and to L5 within the barrel column, which also have input from L4 and also direct thalamic input from VPM as do L4 neurons of course.

Trachtenber *et al*. which will not be repeated here, but will be supplemented now by continuing with the redaction of Petersen.

[7] Uncaging glutamate, the most widely distributed excitatory neurotransmitter, is done by photostimulation here layer by layer, which activates the release of glutamate. The use here is a typical use for mapping excitatory glutamic connections.

PLASTIC IN THE BARRELS

Early (window of a few days after birth) destruction of whisker follicles is accompanied by failure of the development of the corresponding barrels which is unaffected by genetic destruction of NMDAR[8] (Iwasato *et al*., 2000). Petersen considers that thus NMDR cannot be important for the developmental sensitivity to deprivation and that the critical period to change the mainly genetically determined large-scale map of the barrel field only lasts until postnatal day four (p. 345).

However plasticity can be supported on a smaller scale. Dendritic filopedia and spines grow in response to LTP from strong synaptic input which implicates them in synaptic plasticity. Injecting the Sindbis virus with its gene for a fluorescent green protein (SIN-EGFP) onto a small area of barrel cortex and using a two photon scanning electron microscope (2PLSM) in vivo to examine the morphodynamics of dendritic filopodia and spines in L2/3 (the limit of the focusing depth of the 2PLSM being approximately 600 µm), Lendai *et al*. (2002) found a critical period for robust sprouting in the young adult rat.

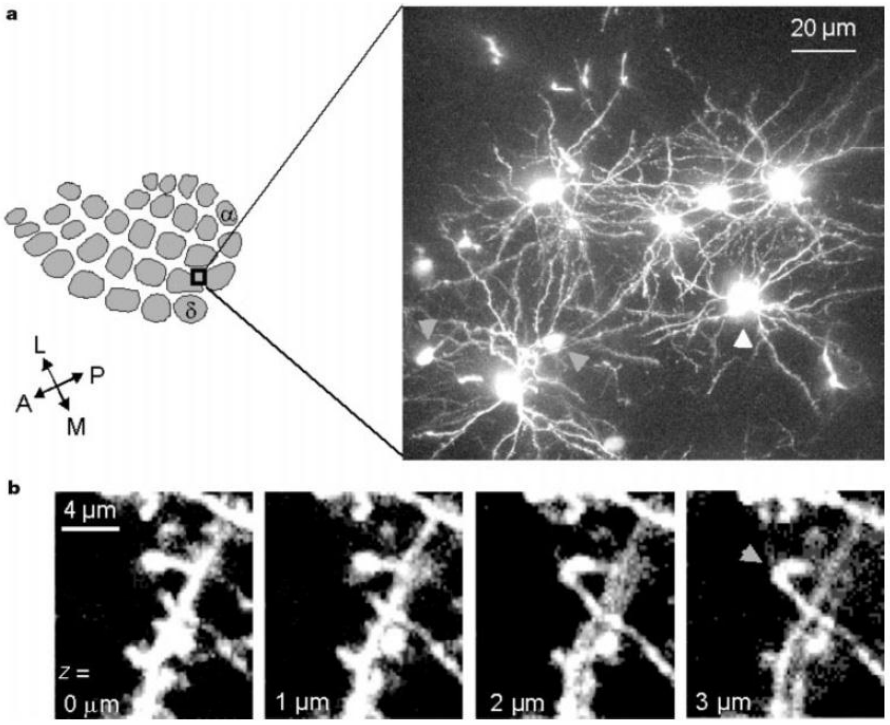


Figure 1 High-resolution imaging of barrel cortex neurons infected with SIN–EGFP *in vivo*. **a**, Left, schematic representation of the barrel field. Injections were made along the medial edge. Right, 2PLSM image of cluster of infected layer 2 neurons (white arrow heads) with basal dendrites (P11, 2 days after infection; projection of 30 sections, 220–280 µm below the surface of the brain). Note the cross-sections of thick apical dendrites belonging to deep pyramidal cells (grey arrowheads). **b**, High resolution 2PLSM images showing apparent contact between a dendritic segment and an axon. Four optical sections separated by 1 µm are shown.

From Lendvai *et al*. (2000), Figure 1. High resolution 2PLSM of dendritic and axonal aborizations of L2 pyramidal neurons of barrel column of a rat.

Diamond *et al*. (1994). Glazewski & Fox (1996), and Fox *et al*. (1996) have shown these structures of L2/3 pyramidal neurons to exhibit experience-dependent plasticity in adult rat.

[8] NAMDR, the receptor for binding N-methyl D-aspartate, implicated in synaptic plasticity for learning and memory.

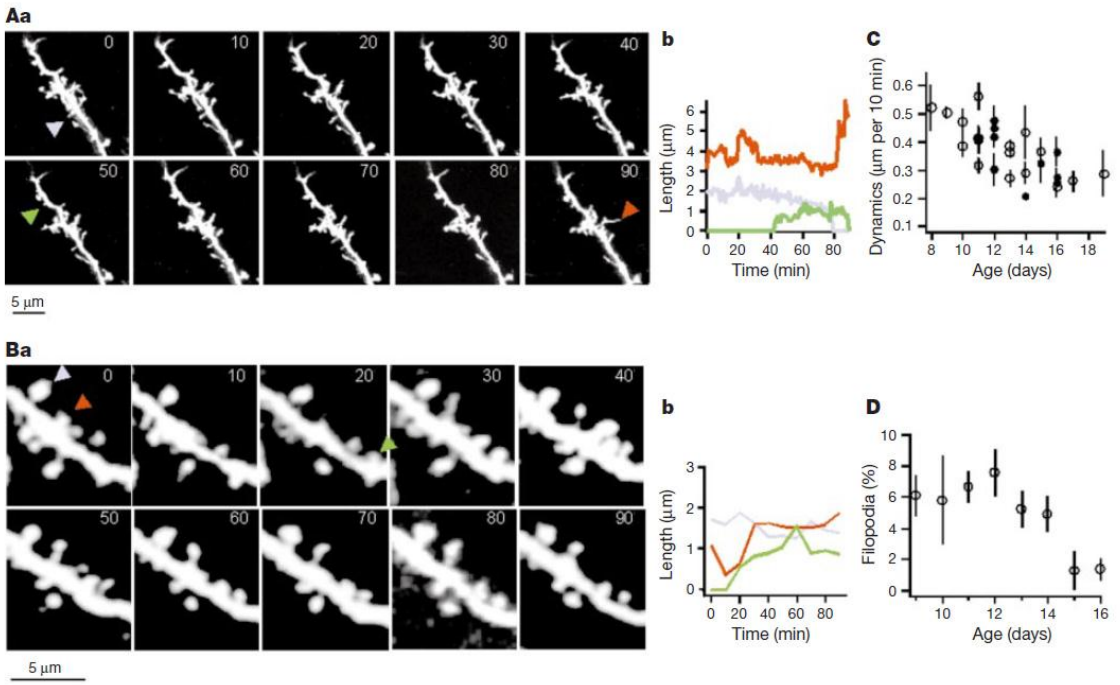


Figure 2 Motility of dendritic protrusions and their developmental regulation. **Aa, Ba**, Time-lapse image sequences showing growth, retraction and other shape changes of dendritic protrusions (time stamps are in min). Coloured arrows point to protrusions that are analysed further in the right panels. Conditions: **A**, imaging rate 1 min^{-1}, P11, control; **B**, imaging rate 1/10 min^{-1}, P17, control. **Ab, Bb**, Time courses of length of selected protrusions. **C**, Development of motility of protrusions. Measurements in barrel cortex o control animals (closed circles) and outside barrel cortex in deprived animals (open circles are shown. **D**, Fraction of protrusions classified as filopodia (length >4.5 μm).

From Lendvai *et al*. (2000), Figure 2. Spines and filopodia are very motile *in vivo*. Time lapse (10 minute intervals) 2PLSM photography of growth (orange) and retraction (gray) and both (green). This age range showed the greatest motility of the filopodia and spines, which not only grew and retracted, but appeared and disappeared within these short tens-of-minute time-spans.

Lendvai *et al*. examined the effect of sensory deprivation on this motility. The examined three age groups, post-natal days (P) 8-10, 11-14, and 14-16, that is just before, during, and after the period of great (400%) increase in number of synapses. They found that experience (sensory deprivation via all large-whisker removal) attenuated motility only during P11-13, and this effect was restricted to the barrel cortex (p. 878). Receptive fields as revealed by microelectrode measurements of PSPs with single whisker removal showed fine tuning in controls, but loss of principal whisker response (how?) but increased response to adjacent whisker stimulation, a broadening of receptive field. Spontaneous PSP are not affected. They conclude that 'sensory deprivation does not modulate synapse number itself, but perturbs the experience-dependent rearrangement of synaptic connections required to form precise sensory maps (p. 880). It would seem that normal experience must play a critical role in the largely genetically programmed laying down of microcircuits during this critical period of development (My conjecture, not theirs.).

Whisker trimming depresses the L4 input to L2/3 neurons (Shepard *et al*., 2003, see their figure in Petersens's Figure 4C above) which thus fire, presumably due to paralemniscal inputs, before rather than after action potentials arriving from L4 axons, thus preventing a Hebbian sequence for spike-timed plasticity (Allen *et al*., 2003).

If we put together Lendai's (2002) broadening of receptive fields with increased responsiveness to spared whiskers (Fox, 1992, 1996; Diamond *et al*., 1994; Glazweski & Fox, 1996) are we getting a picture of some compensatory microcircuitry modifications? Research by Polley *et al.* (1999) is suggestive. They removed all but one whisker for 28 days in the adult rat followed by 28 days of

allowing regrowth of the removed whiskers. During the deprivation period some animals were always caged, while others were allowed two minutes of exploration in a novel environment evey 3-4 days. In the control group the response to whisker stimulation spread over a larger area of barrel cortex during the deprivation period, but reversed to a more restricted area as in the pretest conditions. The novel experience of the other rats caused a restriction of the responsive area of the barrel cortex, which also was reversed during the recovery (whisker growth) period. Does this suggest the possibility that the exploratory experience, acting on faster time scales than the experiential deprivation plasticity, may have involved a more learning/memory type of experience that allowed the brains algorithms to collect the related synaptic changes to geographically smaller barrel regions? Could amalgamated regions involved in the sensorimotor learning and mapping be involved, with the sensory processing using less recruitment of the columnar algorithmic redundancy? Could a paralemniscal broad arousal mechanism involving a lot of cortex prove less efficient than a lemniscal process in fine tuning a discriminative learning process?

As mentioned earlier, slow wave dendritic PSP waves can be more significant than action potentials. Crochet and Peterson (2006) using VSD imaging showed that slow large propagating waves (Ferezou *et al*., 2006) of quiet wakefulness gave way to low variance membrane potential changes in L2/3 pyramidal cells. (See Petersen, 2007, Figure 7 infra.)

Petersen suggests that sensory-motor loops at both brain-stem and cortical levels (including barrel to S1 connections) may amplify cortical responses that might explain differences in barrel activity during active exploratory whisking versus passive whisking. Monosynaptic trigeminal inputs to cortical motoneurons controlling whisker movement causing more active exploration of objects, and thus accounting for the spread of activity across the barrel (pp. 339-340).

Such state-dependent modulation of sensory processes comes closer to the kinds of temporal events required for learning and memory than the experience-dependent (deprivation and developmental) epigenetic processes. To this end, let us look at some learning experiments to show promise for use in the study of neural substrates for learning related to these studies of experience-dependent plasticity with the model somatosensory system.

Some experiments involve classical (Pavlovian) conditioning. An interesting advantage of classical conditioning, such as eye-blink conditioning, is that it is very rapidly learned. One trial often suffices (Abraham, 1967; Diamond & Weinberger, 1986, 1989; Estes, 1960; Mowrer, 1947; Voeks, 1952; Weinberger *et al*., 1984). Classical conditioning of the eyeblink to whisker deflection as the CS has been demonstrated in rodents for both delay conditioning (The US is delivered during the end of the CS presentation; Das *et al*., 2001) and trace conditioning (the CS is off for an interval before the US comes on; Galvez *et al*., 2006, 2007; Leal-Campanario *et al*., 2006). In their first study, Galvez *et al*. (2006) showed that by cytological examination of barrel cortex that there was a row specific 'expansion', which they suggested might be due to hippocampal and forebrain-dependent trace conditioning. In their second experiment they lesioned barrel cortex before conditioning (acquisition) or after (retention). Both groups exhibited large deficits, leading them to conclude that "the barrel cortex Is a site for long-term storage of whisker trace eyeblink associations."

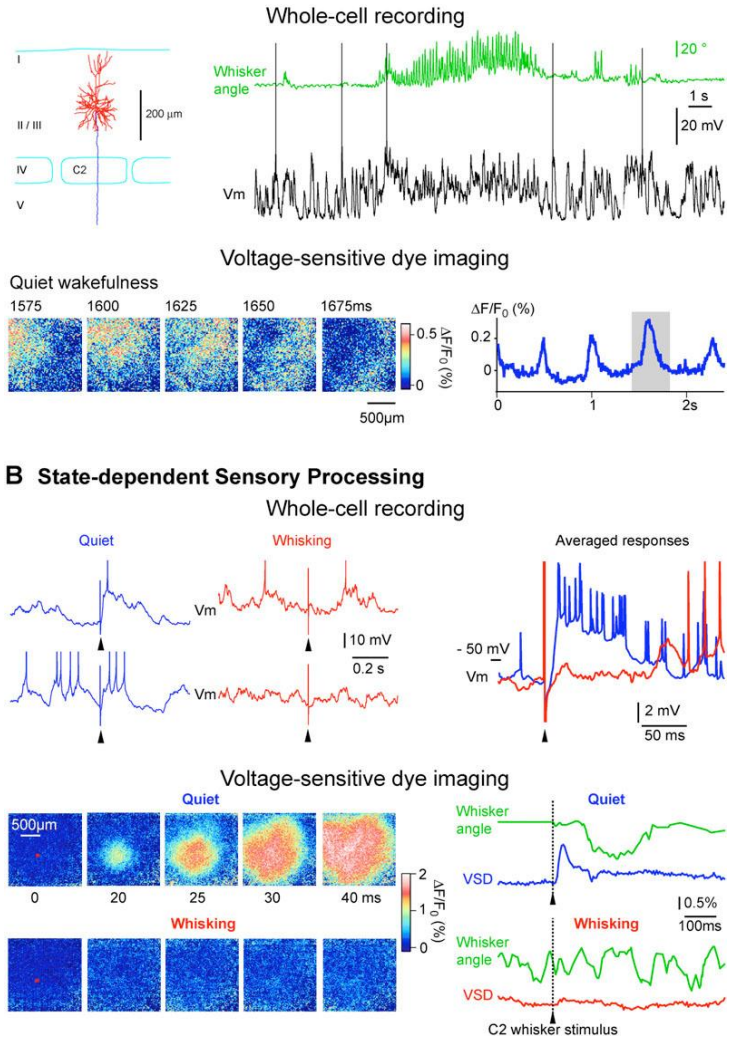


Figure 7 (and text) are from Petersen (2007).

State-Dependent Processing of Sensory Information

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(A) Whole-cell recordings from awake mice during quantified spontaneous whisker-related behavior reveal striking state-dependent changes in membrane potential dynamics (upper panels). A layer 2/3 pyramidal neuron located in the C2 barrel column (left) shows slow large-amplitude membrane potential changes (black trace, membrane potential, Vm) when the C2 whisker is not moving (green trace, whisker angle). During active whisking the membrane potential depolarizes, and the slow oscillations are replaced by higher frequency fluctuations. Voltage-sensitive dye imaging of mouse barrel cortex during quiet wakefulness reveals that the spontaneous slow oscillations occur as propagating waves of depolarization spreading across the neocortex (lower panels). The images (left) show a wave spreading from upper-left to lower-right in the field of view, and the time-course of fluorescence changes are quantified across a small central region of interest (right, gray shading indicates the time of the images).

(B) Passively applied brief deflections of the C2 whisker evoke different cortical sensory responses during different spontaneous whisker-related behaviors. Whole-cell recordings (upper panels, action potentials are truncated to allow an expanded y axis) show that the depolarizing sensory response is strongly reduced during active whisking (red) compared to during quiet wakefulness (blue). This statedependent reduction in sensory processing is not limited to individual neurons but is a network property, which can also be imaged with voltage-sensitive dye (lower panels). Passively evoked sensory responses during quiet wakefulness have large amplitude and spread across large cortical areas, whereas the response is smaller and more localized during whisking. The red square on the images at 0 ms indicates the region of interest centered on the C2 barrel column from which voltage-sensitive dye fluorescence changes are quantified in the adjacent traces (lower right).

The separation of the two stimuli in trace conditioning requires participation of more than brainstem and cerebellar processes which are important in delay conditioning (Clark *et al*, 1984; Mauk & Thompson, 1987). These additional areas include some in the diencephalon, e.g. medioldorsal thalamus (Powell & Churchwell, 2002) and in forebrain, e.g., hippocampus (many studies including Clark & Squire, 1998; Weiss *et al*, 1999; Takehara *et al*., 2002; Tseng *et al*, 2004), anterior cingulate cortex (Han *et al*., 2003), and medial prefrontal cortex (Frankland *et al*., 2006; Takehara *et al*. 2003). Hippocampal lesion made 30 days after conditioning failed to affect the conditioned response, suggesting the importance of neocortical loci for long term trace conditioning (Takehara *et al*., 2002). Models (Eichenbaum *et al*., 1992; Squire *et al*, 2004) suggesting the neocortex, based in part in discrimination training (many, but they include Diamond & Weinberger, 1986 & 1989 for auditory discrimination, and Jenkins *et al*., 1990, and Krupa *et al*., 2004, for tactile discrimination).

This brings us to operant learning. In this regard, it is interesting that learning to locate and jump to a platform can be performed with a single whisker and an intact barrel cortex (Hutson & Masterton, 1986)[9], perhaps utilizing barrel-cortical maps (Harris *et al*., 1999). Krupa *et al*. (2004) studied aperture discrimination in mice using microelectrode recordings. (Figure 9 from Petersen follows.)

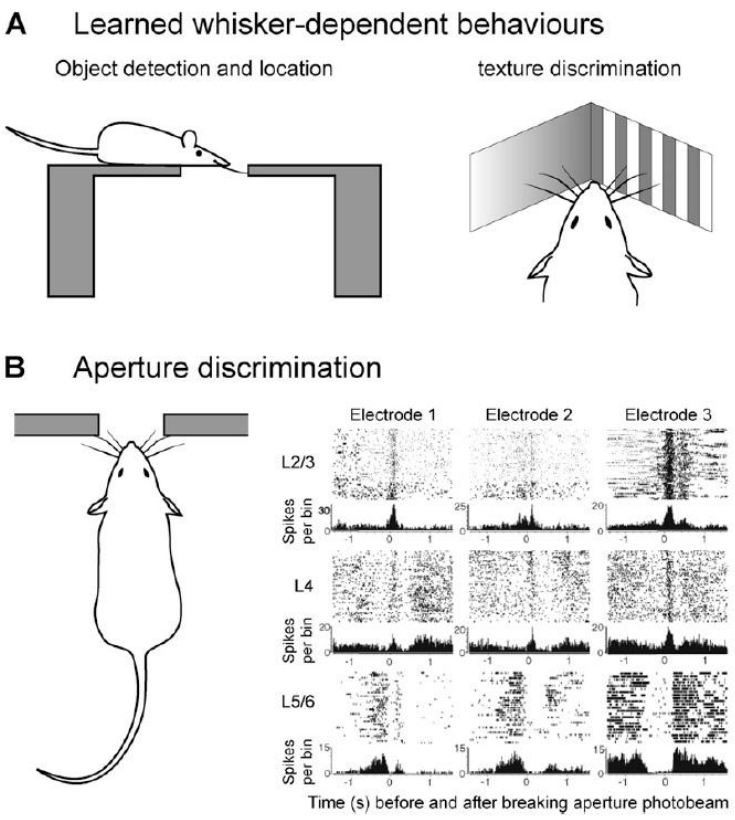

Figure 9. Learned Whisker-Dependent Behaviors

(A) The rodent whisker sensorimotor system performs two classes of behavioral tasks: location of edges and discrimination of textures. Edge detection and location forms the basis of the gap-crossing task (left) where the rodent must reach across a gap with its whiskers to locate a target platform where a reward is placed. Rodents are also able to discriminate textures using their whiskers (right), and quantitative behavioral measurements suggest that texture discrimination by the whiskers equals the performance of the human finger tip.

(B) The first recordings of neuronal activity during learned whisker-dependent behaviors have provided interesting results. Rats were trained to perform a bilateral edge-location task, where the animal must determine the width of an aperture to receive a reward (left). Recording of cortical action potential activity during execution of this learned behavior showed that action potential firing rates changed during different phases of the task. Most surprisingly, infragranular neurons often showed elevated firing rates before the rat entered the aperture, suggesting interesting top-down input to somatosensory cortex.

(B) is modified and reproduced from Krupa et al. (2004) with kind permission from *Science*, AAAS.

The top-down suggestion of Petersen at the end of his text for the figure, reminds us also that there are direct sensory inputs to the motor cortex along with S2 connections, which assist in the control of

[9] For brief movie, use link at reference for Petersen (2007). It requires QuickTime Player7 or other player with an appropriate codec. Make sure to start it at the beginning in order to get the whole sequence of initial exploring and jumping followed by a slow motion of the exploration. This movie is only a few seconds long, but I love it.

whisker behavior. Other tactile discrimination studies have also been performed that also show the important participation of barrel cells in the thalamocortical circuits. Von Barrel cells increase their firing with texture discrimination (von Heimendahl *et al*., 2007). Within in a thalamocortical circuit (VPO-S1), neurons at both levels responded more between the presentation of a stimulus and reward delivery using Krup'a task when reward was response-contingent than when given freely, that is, no discriminative response was required (Pantoja et al. 2007).

O'Connor et al., (2010) recorded from barrel neurons independently of their spiking activity using cell-attached[10] electrodes and two-photon calcium imaging in object discrimination in head-fixed mice. Their Figure 1 follows:

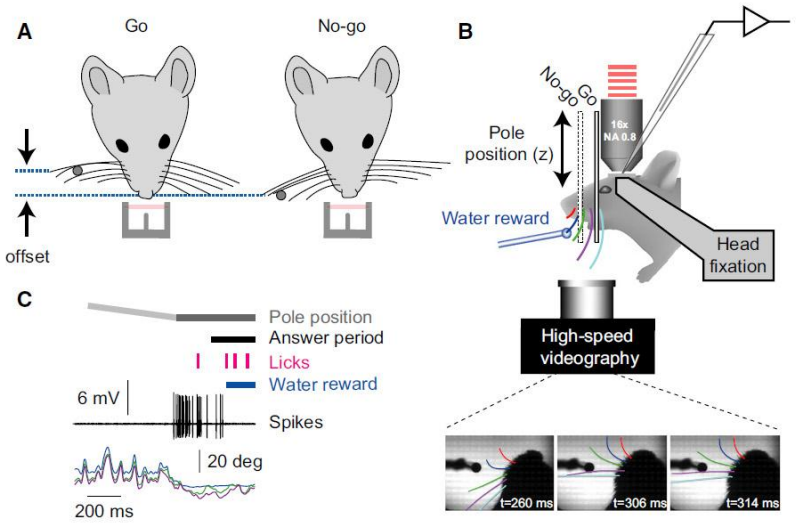

Figure 1. Cell-Attached Electrophysiology and Population Calcium Imaging during a Head-Fixed Object Localization Task

(A) Behavioral task. On each trial, a pole was presented to one side of the mouse face in either a "go" or a "no-go" position. The go and no-go positions were offset (by 4.29 mm) along the anterior-posterior axis. A "lickport," comprising a water spout for reward delivery and an LED/phototransistor pair for recording licking, was placed in front of the mouse. The mouse had to use its whiskers to determine whether the pole was in the go or no-go position to either make (go) or withhold (no-go) a lick response.

(B) Schematic of apparatus. On each trial, the pole was moved vertically into reach of the whiskers, into either the go or the no-go location. High-speed video measured the positions and shapes of whiskers as they explored the pole (bottom image panels). Simultaneously, loose-seal, cell-attached recordings measured action potentials from single neurons in barrel cortex. Alternatively, two-photon microscopy measured activity-dependent fluorescence changes using a genetically encoded calcium indicator.

(C) Example go trial. Light gray slanted bar at top indicates that the pole is in motion; dark gray horizontal bar indicates that the pole is at the end of its range and in reach of the whiskers. The black horizontal bar indicates the start of an "answer period" in which the mouse must either make or withhold a lick response (see Experimental Procedures). The mouse made several licks (magenta ticks) and received a water reward (horizontal blue bar). The cell-attached recording (high-pass filtered) shows a burst of spikes that preceded the lick response of the mouse. Whisker position (bottom) reveals the motor program underlying object localization. See also Figure S1.

While all these studies are highly useful, since several in discussing the aspects of the learning situations have pointed to state-dependent aspects of the behavioral situations, it would seem that freely moving behaviors in as natural a setting as possible would be of the greatest value. The amazing advances in the technologies of morphological, electronic, and genetic measurement and manipulation hold much promise for moving in such a direction, although at present, many of these technologies each have their limitations, especially in getting to multiple areas the deeper in the brain.

A Brief Overview

The discovery of the columnar and microcolumnar organization of neocortex has led to great advances in understanding sensory, sensorimotor, and plastic processes. Many features of macro and micro level organization are clearly defined by genetic and epigenetic controlled development, with critical periods involved in particular aspects of their development, and with experience-

[10] Also known as patch-clamp electodes which record activity of single ion channels on the cell membrane, developed by Neher & Sakmann for which, along with their research findings, they received a Nobel. See Hamill, Marty, Neher, Sakmann, & Sigworth, (1981) and their autobiographies in *Les Prix Nobel 1991*

dependent behaviors participating in many aspects of their development, and providing opportunities for their adjustment to adverse events, such as developmental or environmental sensory deprivation. Short and long-term learning and memory aspects depend on Hebbian synaptic plasticity distributed over millions of synapses which depend on morphological and electrotonic changes as well as action potentials, with inhibitory influences sculpting a fine tuning of this plasticity. While many of the venues for these synaptic changes are yielding to investigation, one cannot but be struck by the innumerable questions and conjectures involved in every investigation no matter the fantastic revelations they reveal.

Systems-complexity modeling is another development, both of complex dynamical systems and networks that is likewise leading to great advances neuroscience, and the interplay between theory and research is of critical importance. To this end, the Blue Brain Project, and other attempts to reverse engineer virtual neural systems seems not as fanciful as it might have seemed at first blush, for its limitations will be very instructive in guiding future research for the missing details. Despite all the advances that have been made, it is clear we are constantly on the thresholds of new bifurcations in our understanding of the brain and the mind.

Dedication

A final comment on the nature of neuroscience.. This modest narrative of but one aspect of neuroscience revealed five well-deserved Nobel Laureates among its authors. What is so fantastic about this field is that there are hundreds of people cooperating in it, and most of them seem as or even more gifted that those who have been laureated, and one has to consider that these individuals must be proxies for the many individuals who have developed this technical and research enterprise. Most seem quite modest about their accomplishments as they realize they are part of a very sophisticated and exciting field. I would urge readers to consult their works, as they are more immersed in this work than I. 26 September 2011[11]

[11] This review is a very rough draft for review by friends for suggestions for improvements, and is not available for public distribution, and permissions to use material has not yet been sought from other authors and publishers, which would be sought in the should this review seem worthy of any kind of academic publication. This review was prompted by a remark of my friend Mark Filippi on the CHAOPSYC discussion group about knowledge in microcircuits which in turn was prompted by a press release from the Markram group that was interpreted rather extravagantly regarding implication of microcircuits having genetically laid down complex mental state. This was a great variance with the realistic reports of their very sophisticated research and modeling programs.

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Appendix 1 A Review of A Few Basic Milestones in the History of Neuronal Specifity, Cortical Columnar Organization, and Plasticity

There is a long history even skipping going back to Aristotle) of the localization of function in the brain, swings back and forth between specificity and distributed processes. Gall and Spurzheim's phrenology being for specific localization, *action proper,* while Flourens' *action commune* allowed unitary action within four major subdivisions of the nervous system (1824). The work of Broca (1861), Fritsch and Hitzig (1870), and Ferrier (1876) yielded evidence for specificity that earlier research tools were unable to discover. Karl Lashley's (1929) m*ass action, equipotentiality,* and *vicarious functioning* were based on effects of cortical ablation on learned behavior.

Mass action refers to the finding that behavioral losses were dependent on the amount of cortex destroyed but not the location of the ablations. Equipotentiality refers to the fact that a habit that is lost by complete destruction of an area may be unaffected when a small part of the area was not destroyed. Vicarious function, previously described by Franz (1921), refers to the fact that a habit may be restored by learning after its destruction by using areas not used in the original learned task. Interesting with respect to the present discussion on columns and minicolumns, his work with Clark led him to deny a functional role for the cortical layers (Lashley & Clark, 1946).

These issues are now somewhat resolved with the recent renaissance in research on distributed integrative neural networks enabled by more precise research tools in recording, stimulating, and imaging in the brain of behaving organisms as well as in in vitro and invivo brain prepartions (Sporns, 2011; Stam & Reijneveld, 2007), just as more precise techniques of electrical stimulation led Fritsch & Hitzig to successful localization that had eluded their predecessors. [For a more adequate early history, see the classic books by Boring (1950) and Hilgard (1987).]

A. Recovery from Transformations of the Perceptual World: Stratton to Köhler

Kepler (1604) wondered why the visual world was perceived as upright despite the retinal image being upside down. Over the ensuing 300 years several commented on this being the wrong view of the matter (pardon me) and that the perceptual world was constructed from the integration of several senses (vision somesthesis, haptics, audition) and their relationship to the body and to behavior (Berkeley, 1709; Molyneux, 1691); Müller, 1938; Volkmann, 1836). Stratton finally tested the matter showing the importance of learning in this integration, by using prism glasses to invert the visual field (Stratton, 1896, 1897). The visual world appeared upside down initially, but in about a week became upright again; removal of the glasses after about a month turned the world back to upside-down, with a shorter time needed for recover to rightside-once more. This paradigm has been investigated with clearer results several times since then (Ewert, 1930; Köhler, 1964) as well as with some similar reversals (Anstis, 1992; Dolezal, 1982; Köhler, 1964). (See Boring, 1950, pp. 677-678; Hilgard, 1987, pp. 138-139.)

B. Neuronal Specificity with no Plasticity: The Pioneering Work of Roger Sperry.

Roger Sperry, renown and for his work on interhemispheric communication, had earlier done some remarkable work on neuronal specificity although the split-brain work is the basis for his Nobel Prize. These earlier studies showed that the development of the connections of optic axons to the optic tectum were highly specific with respect to their position in the retina following their regeneration after cutting the optic nerve in amphibians as tested by both optokinetic stimulation and presentation of flies. Rotation of the eyeballs, and swapping the eyes made for errors in the animal's attempts to catch flies. These changes could not be modified by learning; the deficits continued as long as tested, that is, up to three months. (Grafstein; 2006), Sperry, 1943a, 1943b, 1944, 1945, 1964.)

Sperry concluded "each axon linking only with certain neurons to which it becomes selectively attached by specific chemical affinities" (Sperry 1963, p. 704). Grafstein concluded that the resistance to Sperry's work was due to a number of factors, including the use of lower vertebrates, and to the popularity of mechanical rather than chemical or field factors being involved in embryogenesis (Grafstein, 2006).

C. BRIEF EXCURSUS ON HEBB'S *ORGANIZATION OF BEHAVIOR* (1949)

Not being content with either my poor memory of my reading of *Organization of Behavior* many, many years ago, which was probably inadequate to begin with (and may remain so), or the usual summaries of his principles around which much contemporary research and theorizing revolves, I grabbed my copy to review a few of his principles. There was much underlining but it took more than that to restore my fading memory traces.

1. CHANGE IN SYNAPTIC EFFICIENCY (1949, PP. 62-63.)

Hebb states that some memories are immediately established, some are evanescent, some permanent, the later require structural change in neurons, which would require time, and might be accomplished "If some way can be found of supposing that a [transient, unstable] reverberatory trace might cooperate with the [long term, stable] structural change and carry the memory until the growth change is made." This idea leads to his Neurophysiological Postulate:

"When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."

He suggests that growth of presynaptic axonal knobs (aks 'boutons') are likely responsible, but does not require it as a condition for the postulate. These could occur with or without neurobiotaxis, and he shows a figure from Lorente de Nó to show possibilities of preexisting or neurobiotaxic changes in axonal trajectories supporting such boutons

[See Hebb's Figure 6, Appendix 2-D.]

2. INTEGRATION INTO CELL-ASSEMBLIES (PP. 69-74.)

The basic idea is that when there is afferent convergence of two (or more) cells or systems of cells, that participation in various circuit configuration can facilitate the integration of synaptic change into functional circuits or assemblies. The process may involve critical timing in closed feedback circuits within this process. The process constitutes sensori-sensory associations that build up slowly with repeated stimulation. He gives schematics for visual cortical areas 17 and 18.

[See Hebb's Figures 8 & 9, Appendix 2-D.]

He does not confine the integration into cell-assemblies to closed loops but suggests they can take place in three-dimensional lattices that have connections between different intersections of the lattice, emphasizeing that "the *specificity of such an assembly of cells in* [areas] 18 or 20, *to a particular excitation in* 17, *depends on convergences*." (pp. 72-73.) For reverberations to last sufficiently long enough he proposes multiple pathways, using diagrams similar to current developments in network theory.

[See Hebb's Figure 10, Appendix 2-D.]

3. Perceptual Phase Sequence. (chapter 5 & remainder of the book).

Complex perception he conceived of as an "ideational"series, a sequence of cell-assemblies, each associated with motor excitations intervening between the assemblies in the sequence. These he called "phase sequences". I propose not to elaborate them further, but do want to mention his attitude toward the status of the theoretical scheme. He says he has established that:

*"*A bridge has been thrown across the great gap between the details of neurophysiology *and the molar cocnceptions of psychology. The bridge is definitely shaky in the middle, but it is well*

While much buttressing has occurred from this schema in the years since the *Organization of Behavior* was published, there is much yet to be done. This paper reviews a little piece of the contemporary bridge construction, which in turn points to some future trajectories for its path.

[return to text at Hebb]

D. The Discovery of the Functional Significance of Cortical Columns and Minicolumns with Microelectrode Recordings from Single Neurons: Vernon B. Mountcastle .

Vernon Mountcastle and his colleagues (Mountcastle, 1957; Mountcastle *et al*., 1955, 1957; Powell & Mountcastle, 1959) discovered the functional significance of the columnar arrangement in primary somatosensory cortex in cat and monkey neocortex (S1). They found segregation of submodality properties (somesthetic and haptic properties) for columns that served a given receptive field. These columns are perpendicular to the surface of the cortex, and about 200-800 µm in diameter, depending on species and cortical areas. The dominant cell type are the familiar pyramidal cells running vertically the length of the six layers of the column, and containing huge apical and basilar dendritic branching whose various zones segregate specific and nonspecific sensory as well as transcortical afferents (Scheibel & Scheibel, 1970, 448-450; Figure 5, 6, 7). Within the column, these cells have nearly identical receptive fields, irrespective of their layer. Other cells (Golgi type II) along with recurrent and transcortical inhibitory influences assist in the integrative aspects of the column.

[Go to Scheibel & Scheibel's Figures in Appendix 2]

Mountcastle (2003) mentions that "many anatomists had described cords of cells oriented normally to the pial surface, like those in the human auditory cortex described by von Economo who first used the word column to describe them (von Economo and Koskinas, 1925)." Also that "Lorente de No had described, in 1949, synaptically linked, trans-laminar, chains of neurons in the rodent cortex, which he postulated to be an elementary unit of the neocortex". Now referred to as minicolums, 80-100 in number, 40–50 µm across, into which the columns are partitioned. Mountcastle was responsible for discovering that feature extraction was a function of this partitioning of the column into minicolumns (Mountcastle, 2003). These minicolumns show exquisite modular cytoarchitecture which provides what is now a major laboratory preparation for the analysis of properties of sensory, motor, and transcoritcal afferent and efferent connections among these networks of cells, and their segragative and integrative functional organization.

[return to text p2]

E. The Pursuit of the Segrgation and Integration of Visual Information within Cortical Columns and their Plasticity: Hubel & Wiesel.

Hubel and Wiesel made an accidental but astute observation when they undertook to pursue neural studies of receptive fields of neurons in the visual system following the successes of Mountcastle within the somatosensory system. Expecting to find perhaps on-center-off-surround or off-center-

on-surround receptive fields for black or white spots in the striate cortex similar to those in the lateral geniculate of acutely prepared cats, they were puzzled until they realized that some of the neurons were firing not to the spots used to project the stimuli to the renina, but to the shadow of the edge of the slides as they passed by the lens of the projector, rather than to the spots on them which were intended to act as stimuli—see their movie at Hubel and Wiesel Cat Experiment. These led to a series of systematic studies of neural responses to particular aspects of visual stimuli, edges, motion, direction of motion, contralateral and ipsilateral presentation, and binocular aspects, concluding that same cells were simple and some complex and that there was a hierarchy of taking this segregation of stimulus properties into the integration of these properties for a reconstruction of the stimulus.

1. 'Simple' visual receptive fields of striatal cortical neurons.

The receptive field for a given cortical neuron is that area of the retina which, when stimulated, produces a change in the rate of firing of that neuron (recorded using extracellar microelectrodes; then a recent advance in neuroscience technology). For 'simple' fields, different parts of the field could have excitatory effects, and in other parts inhibitory ones, the parts being mutually antagonistic (no response when both areas were stimulated). Within each area of the receptive field, the response increased with the amount of the area stimulated, but fell off if the stimulus was too big due to its invading the other, antagonistic area. Unlike the concentric receptive fields of retinal ganglion and geniculate cell, the cortical cells were adjacent to each other separated by a straight line (the axis of the receptive field). Movement was often an effective stimulus, sometimes the only effective stimulus, and its use sometimes speeded up finding features of the receptive fields.

[See Hubel & Wiesel's Figure 2 and Movie, Appendix 2]

2. Complex Receptive Fields

There were many types of more complex receptive fields. Most of these differed in not having summation (that is not an increasing monotonic function) within a whole excitatory or inhibitory area of the field except within a narrow slit-type stimulus' area. Some showed 'off' responses' as well as 'on' responses'. One cell of this type showed responsiveness only to a horizontal bright bar, with 'off' responses to stimuli in the upper half of the its field, and with 'on' responses to those shown in the lower half, with both 'on' and 'off' to stimuli at intermediate positions, and none to stimuli covering either the whole upper or lower half of the receptive field.

[See Hubel & Wiesel's Figure 3, Appendix 2]

They found that "all units have responded to visual stimulation, though it has occasionally taken several hours to find the retinal region containing the receptive field and to work out the optimum stimuli. Some cells responded only to stimuli which were optimum in their retinal position and in their form, orientation and rate of movement. A few even required stimulation of both eyes before a response could be elicited (see Part II)." (Hubel & Wiesel, 1962, p. 122.) They also noted that during the 1-9 hours of recording from a cell, no cells showed qualitative changes in their receptive fields (p. 123).

These are but a few of the simple and complex cells they found, but should illustrate the obvious point that the nature of these responses to stimuli in their receptive fields not only show

specificity of response, segregation, extraction, or isolation of features of the stimuli, but that this process would require interaction among many cells.

3. Binocularly Responsive Cells and Ocular Dominance.

Unlike cells in the lateral geniculate most of which respond only to monocular stimuli (such cells being segregated into layers of contralateral or ipsilateral stimulation), many cortical cells respond to stimulation from equivalent positions of the retina of both eyes (Hubel & Wiesel, 1959, 1962). Properties of the organization of the receptive cells were similar for the two eyes. For some cells there was cancelation when there was stimulation of antagonistic regions in the two eyes; for some there was ocular dominance—stronger response to stimulation of one eye—and for some other cells, there was a synergistic increase of response, or response only, if both eyes were stimulated.

[See Hubel & Wiesel's Figure 12, Appendix 2]

4. Cortical Organization

Initially, since electrode penetrations were not always normal to the cortical apical surface, the organization was not characterized as columnar, but cells with similar properties of their receptive fields, such as having the same axes, were characterized as close neighbors (1962, p. 129), but careful examination of the tracks led them to observe "it seems likely that the general shape is columnar" (p. 133). There seemed to be some layering within cortical columns, with simple fields being more represented in layers 3, 4, and 6, and complex fields being most prevalent in layer 2, and absent in layer 4. (p. 139). Thus there is specialization both columnar and by layer. Interestingly for the minicolumn issue, in this paper they note that many columns showed cells with differences in ocular dominance, and they suggest the "The cells could be arranged in nests, or conceivably in very narrow columns." (p. 140.)

In this 1962 paper, they point out the impossibility of studying the receptive fields of all the afferents to a given cortical cell, and suggest that more conjecturing is required to explain the nature of the receptive field of the pyramidal neurons from which they record. For simple receptive fields of cortical cells they suggest an arrangement of on-center and off center geniculate cells as a possibility for the linear receptive field of the cortical cell. They propose a scheme as very tentative; here is an example:

[See Hubel & Wiesel's Figure 19, Appendix 2]

Complex receptive field they construed as the result of inputs from sets of cells with simple excitatory fields. They thus proposed a hierarchy of cortical integration. Besides being very tentative, as with the simple cells, there are more schemes than we can present here; it is suggested that the original papers be consulted for a very rewarding experience. Here is one example:

[See Hubel & Wiesel's Figure 20, Appendix 2]

They next turn to functional cytoarchitecture of the columnar organization to support these conjectures.

5. Cytoarchitectural Considerations and Comparison to Mountcastle and Others.

The lateral geniculate, the main thalamic visual relay station, has fewer cells, with, except for ipsi-contralatera layering, little specialization of their receptive fields with concentric (center and annular surround) of excitatory and inhibitory responding. Cortical cells are organized into columns, with afferents to simple cells from the geniculate, while the afferents for the complex cells are from simple cells within the column. The simple cells are responsible for segregating different aspects of visual information, and the complex cells are responsible for integrating this information into useful perceptual information. Many columns are devoted to a small region of the visual field, each differing in the orientation of the axis of the receptive field.

"Compared with cells in the retina or lateral geniculate body, cortical cells show a marked increase in the number of stimulus parameters that must be specified in order to influence their firing." (Hubel & Wiesel, 1962, p. 145.) Despite this hierarchical tendency toward increased specificity, they point out that the retinal position for complex cells is not as demanding for the complex cells as the simple ones, suggesting that this property satisfies a perceptual advantage for form perception, the need to recognize things independently of their retinal position, that is, their exact location in the visual field. The orientation property is thus "generalized over a considerable retinal area." (p. 146.)

Hubel and Wiesel note that the difference between the two sensory systems studied at that point (1962) with microelectrodes, somatosensory (Mountcastle, 1957; Powell & Mountcastle, 1959) and visual, while they both have columnar segregation of stimulus submodaliies or parameters, there are many more stimulus parameters in the visual system, and there was yet little information on complex integration of stimulus information in the somatosensory system. As incredible as this exacting program was, especially and despite its influence on behavioral neuroscience, it is a different aspect of this research program which won them their Nobel Prize. Rather it was their studies on developmental and behavioral plasticity inherent in this system.

6. Some Aspects of Development and Plasticity of the Visual System: Wiesel & Hubel

These studies involved the effects of monocular and binocular visual deprivation upon both vision and receptive fields of neurons in order to examine parameters of invariant and plastic properties of the visual system. This classic series of papers has been nicely reviewed recently by Constantine-Paton (2008).

At the geniculate level, activity and size were attenuated in cells serving the eye that was deprived monocularly for the first three months of kittens' lives, but for cells serving the normal eye, receptive fields and cell morphology were normal, similar to those of adult cats Similar but smaller changes in histology were obtained when the onset of visual deprivation was delayed for two months, and no changes were observed if the onset of deprivation were begun after three months, suggesting critical periods for the formation of the geniculate level of organization of the visual system. Deprivation attenuated the growth of cells (Wiesel & Hubel, 1963a).

In a second study of visual deprivation in very young kittens they found that "the highly organized behavior of cells in the striate cortex must be present at birth or within a few days of it . . . even in the absence of patterned visual experience." Hubel & Wiesel, 1963.) To me, this conclusion appeared a bit contradictory to that of the first paper which concluded that inhibited growth rather than atrophy was likely responsible for loses of responsiveness and histological properties in geniculate neurons. One could account for this contradiction if three-week patterned visual deprivation in the newborn kittens was less severe than the three-month

deprivation of the geniculate study or if indeed there were atrophic effects in the previous study? In their next paper, they suggested that the solution to this paradox could be due to the monocular innervation of geniculate neurons in contrast to the binocular innervation of cortical neurons [under the assumption that innervation supports development of post-synaptic neurons] (Weisel & Hubel, 1963b, pp. 1011-1013).

This last of the three 1963 papers reported behavioral and striatal responsiveness after monocular deprivation of two-three months in kittens. Deprived kittens showed behavioral and perceptual blindness while the kittens were ambulatory when only use of the deprived eye was allowed. There was also loss of cellular responding, although a few cells respond, and those had defective receptive fields and were restricted so smaller cortical areas (islands'). The normal eye gave normal results. Receptive fields for cells in the striate cortex revealed loss of responsiveness and ocular dominance for the deprived eye. One-two months of normal vision in kittens prior to deprivation produced less severe loss, and deprivation in adult cats produced no abnormalities. The results showed columnar organization. They conclude that "the physiological defect in the deprived kittens represents a disruption of connections that were present at birth." (Wiesel & Hubel, 1963b p. 1017, with similar comments at p. 1011 and in 1965a.)

The first study of three of their 1965 series of papers (Wiesel & Hubel, 1965a) was designed to determine the effects of binocular deprivation on striate responsiveness and perceptual vision but included some binocular tests that showed results typical of previous studies, of loss of responsiveness to stimulation for the deprived eye. For the few cells that were responsive to stimulation of both eyes, there was ocular dominance for the normal eye, and distorted visual fields lacking the orientation sensitivity, and showing brief responding and responsiveness to a small portion of the electrode penetration.

With binocular deprivation, many cells could be driven, though many of those with abnormal receptive fields, principally in lacking sensitivity to orientation. Of the cells responding normally, they were both of the simple and complex types. For a given electrode penetration, dominance and non-responsivity features tended to occur in their own restricted depths of the penetration.

Since the surprising result of the responsiveness of many neurons surviving binocular deprivation, they performed histological examination of the lateral geniculate, which showed the expected result of cellular abnormalities in all layers. Behaviorally, the kittens appeared blind.

They suggest that "The surprising thing was not the extent of the physiological changes, but on the contrary the fact that they were not more severe. . . . it was as if the expected ill effects from closing one eye had been averted by closing the other. Taken together, the [experiments] seem to suggest that early in life the functional integrity of the pathway may depend not only on the amount of afferent impulse activity, but also in the interrelationships between the various sets of afferents." (Wiesel & Hubel, 1965a, p. 1038. They further suggest that this convergent interaction occurs at the simple cells. They suggest the possibility of afferent competition for synaptic dominance at this level.

In their next study which was on the effects of surgically induced strabismus, most cortical cells showed no binocular responsiveness despite normal behavior of the kittens. .Columnar organization of the striate cortex was evident. (Hubel & Wiesel, 1965.) When they studied recovery of function for extended periods after removing visual occlusion, there was little evidence of recovery. They expected some on the basis of other species in clinical or experimental observations had been made, although not with comparable conditions to their own research (Wiesel & Hubel, 1965b). Much work has been done on recovery of function.

These deal with critical periods for disruption and recovery of function, and hold great significance for recovery of function in children.

These studies, employing edge detection, orientation, and ocular dominance from retinal to striatal levels, as well as behavioral aspects and recovery of function, have focused on critical periods for both innate factors and experiential ones in development and atrophy in the visual system. They have demonstrated how properties of the system are segregated at geniculate levels and reconstructed by convergence in the columns of visual cortex, and they ". . . conclude that the animals'' capacity to recover from the effects of early monocular or binocular visual deprivation, whether measured behaviorally, morphologically, or in terms of single-cell cortical physiology, is severely limited, even for recovery periods of over a year (Wiesel & Hubel, 1965b, p. 1071).

[return to text p2]

F. Barrels with Individual Whisker Receptive Fields and Subbarrels with Directional Whisker-Displacement Receptive Fields: T.A. Woolsey & Van der Loos to Simons.

Certain preparations have drawn a great deal of attention due to both ease of access and the clarity of their properties which, for good reason, invite scientific exploitation, e.g.: *Rattus norvegicus*, *Mus musculcomisurius* and its cousins, *Caenorhabditis elegans*. *Aplysia californica*, callosal commissurotomies, college students, insert your own favorites here. And barrels! Thomas Woolsey, son of the famous neuroscientist, Clinton Woolsey, with Hendrik Van der Loos, discovered an important elaboration of the columnar organization of somatosensory cortex. They characterized the structural organization in L4 (S1) as 'barrels' each having a receptive field from one whisker, with an isomorphic correspondence between the distribution of face whiskers and cortex as determined (Woolsey & Van der Loos, 1970). Previous electrophysiological somatosensory mapping had suggested this possibility to them.

Barrels immediately became a model preparation, due not only to this orderly topographic correspondence ("one barrel represents one vibrissa", but also sensory deprivation (damage to whiskers) is performed easily, nearness to the cortical surface makes recording easy, nature of the hairs makes controlling parameters of their movement, i.e., stimulation relatively easy, availability of transgenic mice makes study of biochemical bases of plasticity easier, and lastly, as a specialized column, there is the possibility of investigation of and generalization to other cortical areas (Feldman & Brecht, 2005).

[See Woolsey & Van der Loos, Figure 15, Appendix 2]

Similar to the developmental studies of Wiesel and Hubel, destruction of a hair follicle in newborn mice within a critical postnatal period, led to the atrophy of the corresponding cortical barrel (Van der Loos & Woolsey, 1973). Axonal degeneration studies showed barrel innervation of cortical barrels from the thalamic ventral posterior medial nucleus (Killackey, 1980). Unlike thalamic organization in the visual system, the posteromedial barrel subfield is laid out much as in the cortex (Woolsey, 1978) with the primary leminsical pathway from whiskers to S1 barrel going through trigeminal nuclei, then the dorsal section of the venteroposteior medial nucleus of the thalamus (Diamond *et al*., 2008; Fox, 2008).

Welker (1976) showed by mapping many contralateral parts of the face and bodies of rats with microelectrode recording, that the barrel architecture was widespread throughout the somatosensory neocortex. The mappings showed the corresponding topographical similar to

those from previous studies with evoked potential recordings (Marshall, Woolsey, & Bard, 1941). More sensitive parts of the body were associated with larger areas of cortical representation. Further studies of the full depth through all layers of the somatosensory cortex showed that the barrels were an integral part of columns (Simons ,1978).

[See a nice somesthetic map labeled on a photmicrogaph of L4 of mouse cortex]

With respect to experience-dependent neuronal plasticity, whisker removal causes diminished inhibitory input to a given barrel column which allows increased by excitatory horizontal inputs from neighboring regions, thus taking over larger areas for the neighboring barrels, in which intricate timing of impulses is important (Finnerty *et al*., 1999; Kelley *et al*., 1999). There can be recovery of function from this sensory deprivation. Synaptic dynamics including EPSPs and LTP and LTD[12] are also involved.

"It seems intuitively likely that structural changes at the level of axons, dendrite branches, and dendrite spines underlie some of the long-term plastic changes in the cortex. Axonal remodelling has been reported in lesion-induced plasticity but not (until now) in experience-dependent plasticity,[20] but a recent study by Cheetham et al.[21] found that whisker trimming produces targeted axonal remodelling in spared cortex. Dendritic branching is important during prenatal and neonatal development, is involved in plasticity induced by lesions, but is not involved in experience-dependent plasticity.[22] In vivo two-photon microscopy[13] reveals that dendritic spines in mouse barrel cortex are highly dynamic and subject to continuous turnover, and may be associated with formation or deletion of synapses.[22] It is likely that spine turnover is necessary but not sufficient to produce experience-dependent plasticity, and other mechanisms such as axonal remodelling are also needed to explain features such as savings from prior experience.[21]"[14]

The investigation of more specific features of vibrissal displacement, in particular the angle and frequency of displacement, has led to the characterization of sub-barrel organization of somatosensory cortex (Andermann & Moore, 2006; Bruno *et al*., 2003; Simons, 1985). These studies are similar to Hubel and Wiesel's analysis of receptive fields for orientation of a visual edge onto minicolums. Andermann and Moore refer to the whole column (i.e., not limited to L4) and find not only sub-barrel directional mapping but also an 'interdependence of somatotopic and directional representations' which was also a function of several cortical layers, and in fact some response properties are more robust in L2/3 (p. 549). They emphasize some additional features of this mapping, noting that frequency-resonance representation spans an arc of columns (Anderman *et al*.,

[12] Excitatory Post-synaptic Potential, Long-term Potentiation, Long-term Depression; references to electrical properties of post-synaptic neurons.

[13] Two-photon microscopy depends on a 1931 concept (Goeppert-Mayer), and was developed by Denk in a series of papers (1990-2005) in which fluoresces in the 700-1000 nm (infrared) band are stimulated by two photons that require less energy than single photon flourphores, and the stimulating laser can be focused into a small femptoliter volume, on a femptosecond time scale, allowing high resolution deep-tissue imaging by overcoming formidable image scattering challenges. See Denk & Svaboda (1997) and http://en.wikipedia.org/wiki/Two-photon_excitation_microscopy and Peter (2002). Also Engelbrecht et al. (2008) and Helmchen et al. (2001) for head-mounted in vivo photography! (See schematics)

[14] This quote is from a redaction, adaptation, and updating of Feldman & Brecht, 2005 taken from Wikipedia (Barrel Cortex). The preceding paragraph is a redaction of that redaction, see Feldman & Brecht (2005) reference for the Wikipedia reference information. In the quote, [20] is Chklovskii *et al*., (2004), [21] is Cheetham *et al*. (2008), and [22] is Trachtenberg *et al*. (2002). The revision history shows over two dozen authors.

2004), whisker representation is one-whisker-to-one-barrel mapping, and directional representation is on a sub-barrel basis. Thus different sensory properties converge, similar to Hubel and Wiesel's complex fields, and there are thalamic differences in representation requiring 'thalamo-cortical realignment' (p. 549). Features of plasticity involve ascending projections of L4 neurons to those in L2/3 and horizontal innervation may provide for integration of vibrissal information.

Rats and mice, having poor vision and none of the properties of the visual system that Hubel & Wiesel found in cats and monkey, thus construct a 3D world by a combination of tactile cues, including an 8 Hz oscillatory sweeping of objects with their vibrissae, and this somatosensory mapping displays many similar features of plasticity built using hard-wired small iterative and interconnected synaptic circuits that serve animals with good vision (Petersen, 2007.) It is possible that the evolution of increased amounts of neocortex with its increased number of columns has arisen in evolution in conjunction with increased sensory, perceptual, motor, cognitive and plastic functions, in a punctuated equilbriar fashion as could be expected from bifurcation theory (Abraham, 2010).

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Appendix 2: Figures

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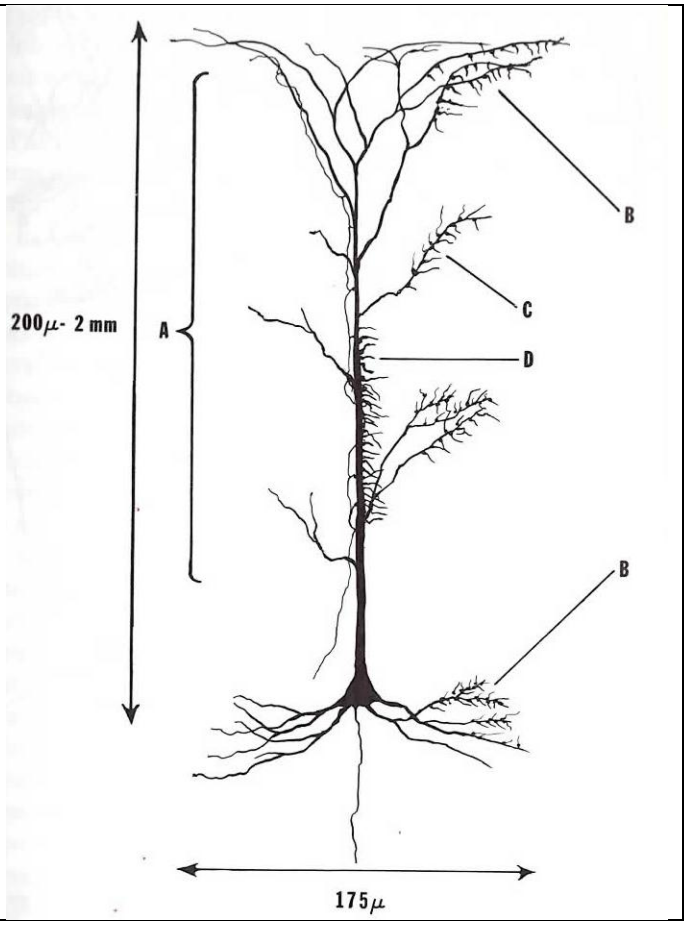
A. SCHEIBEL & SCHEBEL FIGURES 5, 6, & 7.

Scheibel & Scheibel, Figure 5.

The individual cortical pyramid conceived as the simplest modular element of cortex, showing the location of major presynaptic terminal ensembles.

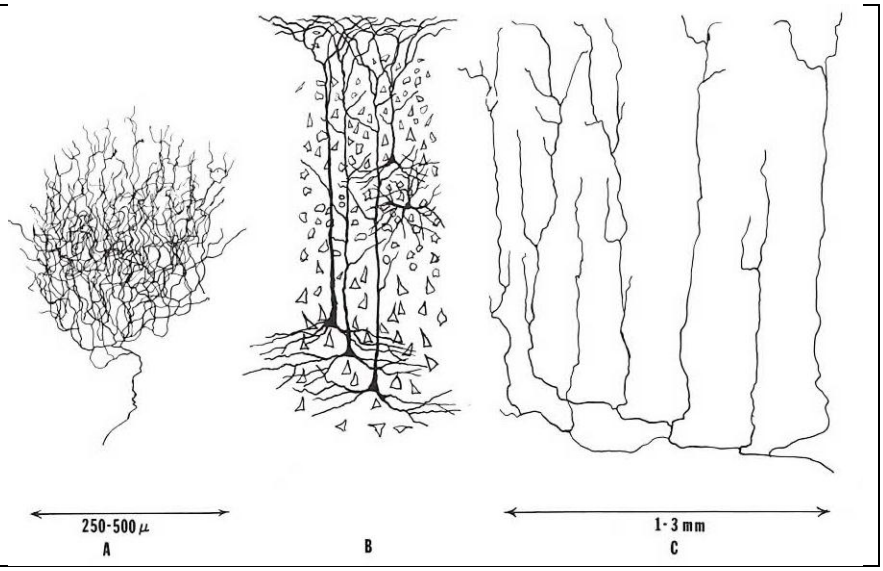
A. Diffuse distribution of nonspecific (brainstem reticular and intralaminar) afferents along the entire vertical dendrite system.
B. Distribution of recurrent collaterals on basilar dendrites and apical arches.
C. Distribution of of callosal (contralateral) afferents on oblique branches.
D. Distribution of specific afferents projection on central third of apical shafts (of L5 pyramids).

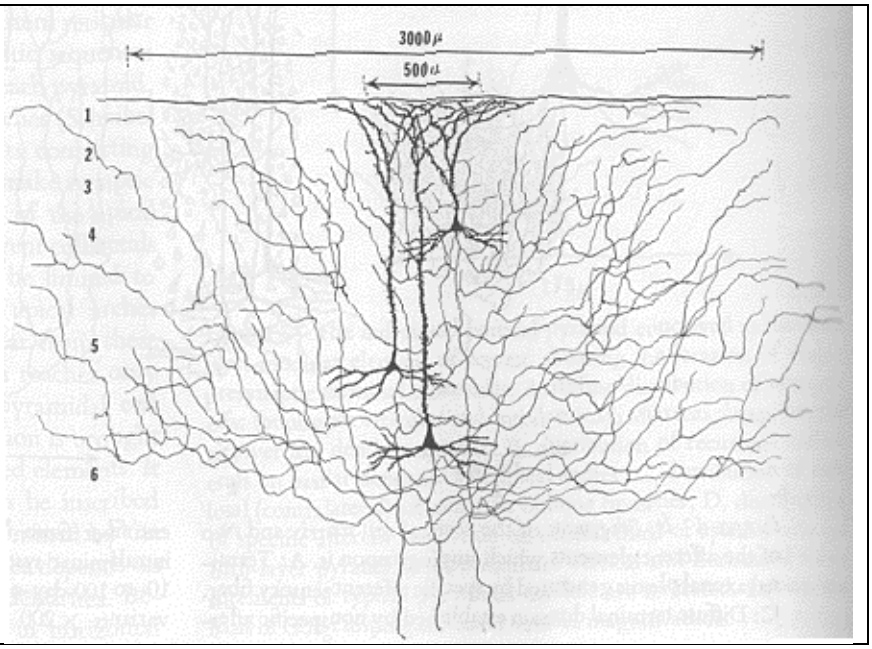
Approximate vertical and horizontal measurements of typical pyramidal module are indicated. Drawn on basis of Golgi impregnations at various magnifications. Such a neuron may receive as many as 30,000 synaptic inputs.



Scheibel & Scheibel, Figure 6.

A. Terminal axonal plexus generated by specific afferent sensory fiber.
B. Fragment of the cortical cell matrix and two of the afferent elements which impinge upon it.
C. Diffuse terminal domain established by nonspecific afferent fiber from brainstem reticular formation of thalamic intralaminar system.



Scheibel & Scheibel, Figure 7. Ensemble of recurrent collaterals [axons] which surround three pyramidal cells in cortex. For any small group of core neuronal elements this may be considered the domain of recurrent inhibition. Drawn from several sections of 60-day cat cortex stained by a rapid Golgi variant . x200	

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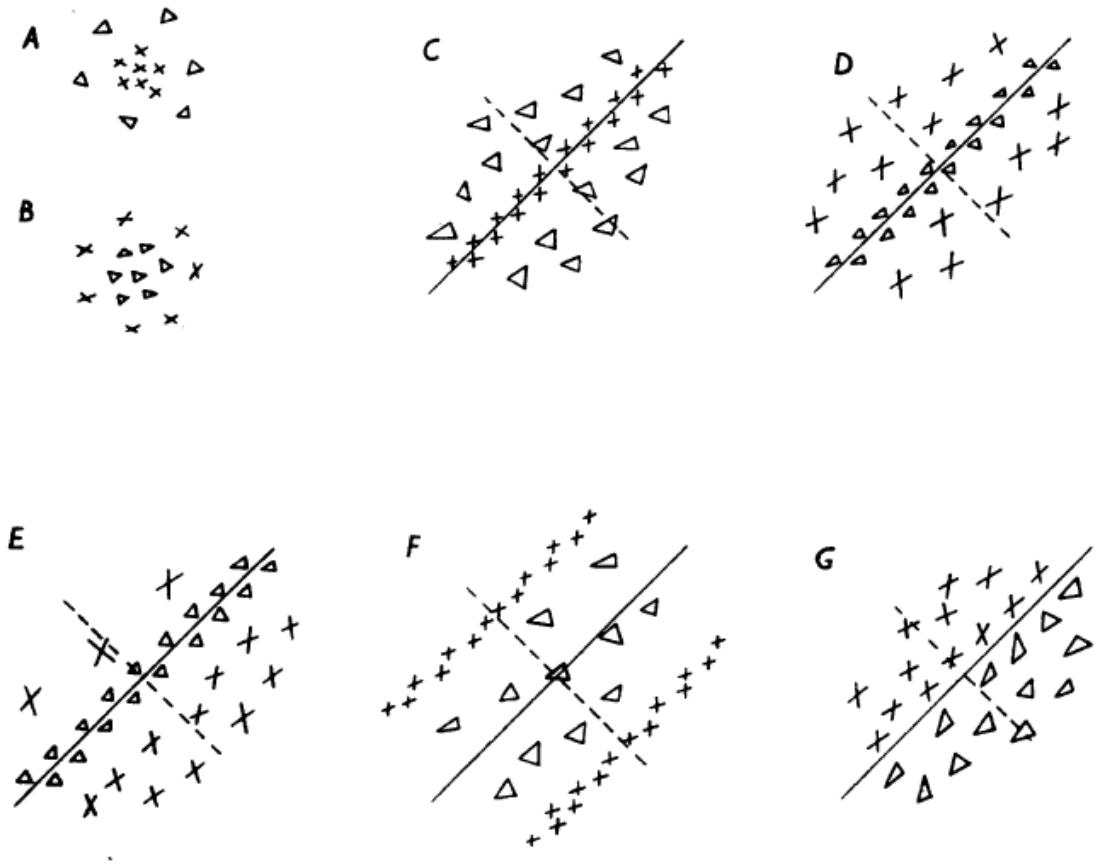
B. HUBEL & WEISEL (1962, FIGURES 2, 3, 19)



Text-fig. 2. Common arrangements of lateral geniculate and cortical receptive fields. *A*. 'On'-centre geniculate receptive field. *B*. 'Off'-centre geniculate receptive field. *C–G*. Various arrangements of simple cortical receptive fields. ×, areas giving excitatory responses ('on' responses); △, areas giving inhibitory responses ('off' responses). Receptive-field axes are shown by continuous lines through field centres; in the figure these are all oblique, but each arrangement occurs in all orientations.

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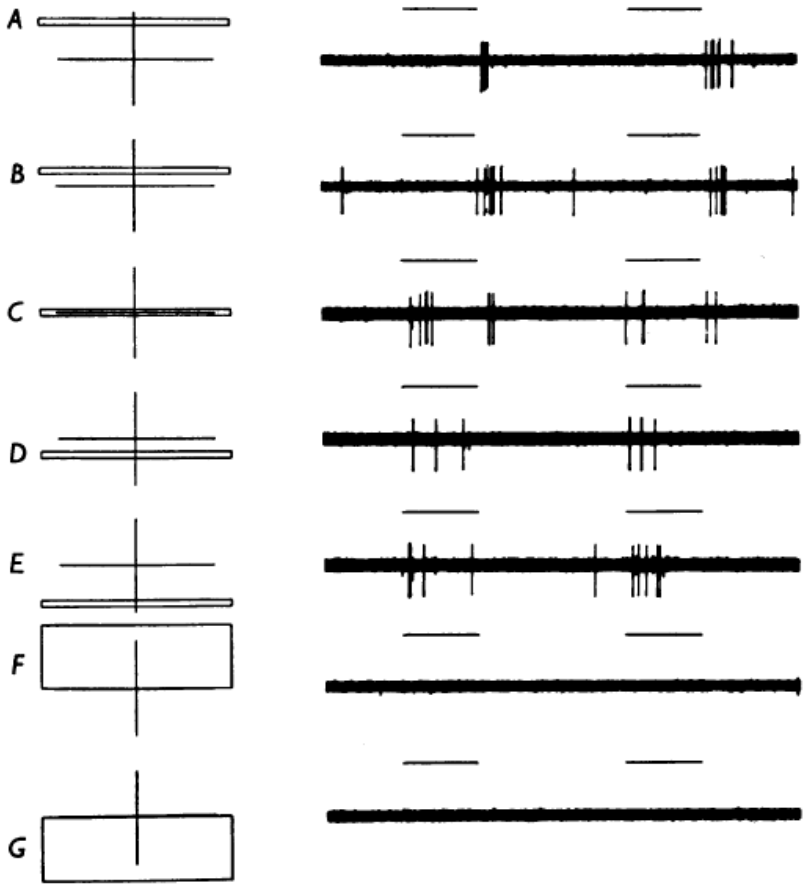

Text-fig. 3. Responses of a cell with a complex receptive field to stimulation of the left (contralateral) eye. Receptive field located in area centralis. The diagrams to the left of each record indicate the position of a horizontal rectangular light stimulus with respect to the receptive field, marked by a cross. In each record the upper line indicates when the stimulus is on. *A–E*, stimulus $\frac{1}{8} \times 3°$, *F–G*, stimulus $1\frac{1}{2} \times 3°$ (4° is equivalent to 1 mm on the cat retina). For background illumination and stimulus intensity see Methods. Cell was activated in the same way from right eye, but less vigorously (ocular-dominance group 2, see Part II). An electrolytic lesion made while recording from this cell was found near the border of layers 5 and 6, in the apical segment of the post-lateral gyrus. Positive deflexions upward; duration of each stimulus 1 sec.

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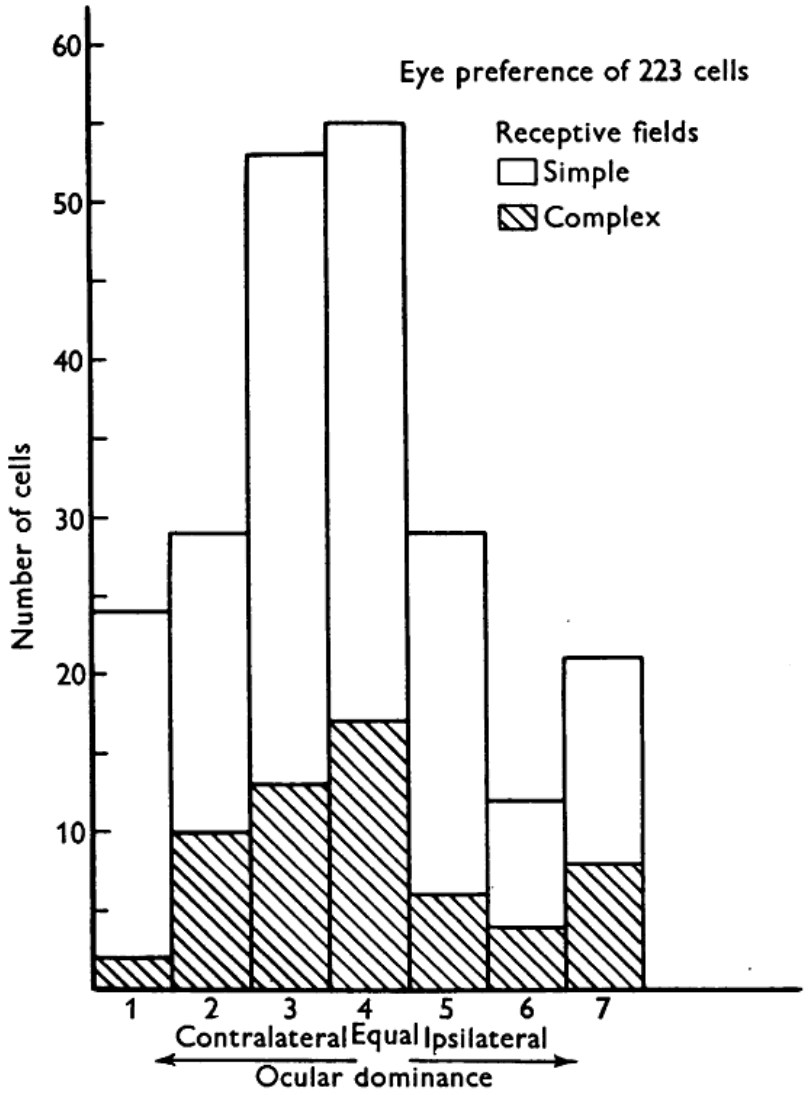

Text-fig 12. Distribution of 223 cells recorded from the visual cortex, according to ocular dominance. Histogram includes cells with simple (white) and complex (shaded) fields.

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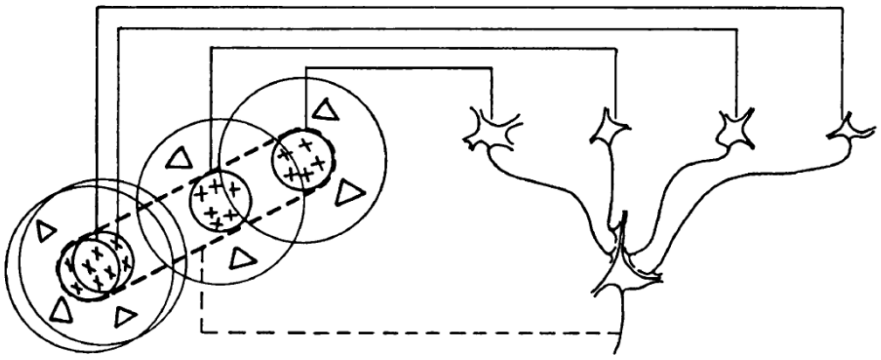

Text-fig. 19. Possible scheme for explaining the organization of simple receptive fields. A large number of lateral geniculate cells, of which four are illustrated in the upper right in the figure, have receptive fields with 'on' centres arranged along a straight line on the retina. All of these project upon a single cortical cell, and the synapses are supposed to be excitatory. The receptive field of the cortical cell will then have an elongated 'on' centre indicated by the interrupted lines in the receptive-field diagram to the left of the figure.

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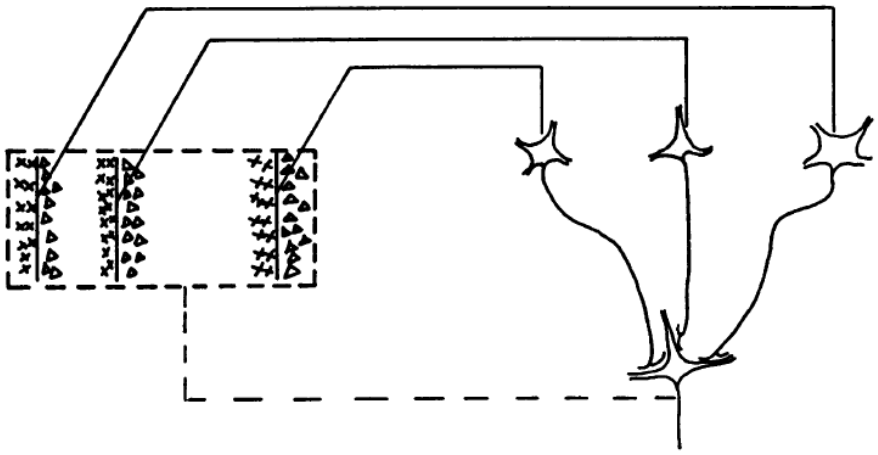
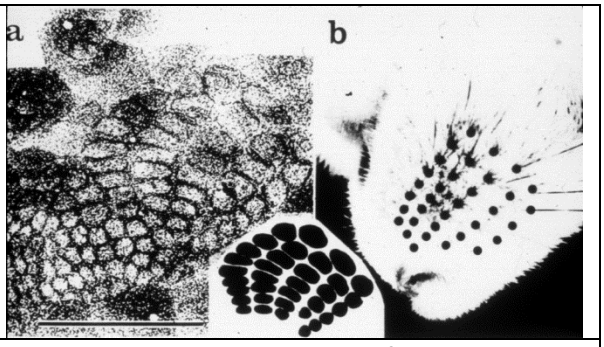


Text-fig. 20. Possible scheme for explaining the organization of complex receptive fields. A number of cells with simple fields, of which three are shown schematically, are imagined to project to a single cortical cell of higher order. Each projecting neurone has a receptive field arranged as shown to the left: an excitatory region to the left and an inhibitory region to the right of a vertical straight-line boundary. The boundaries of the fields are staggered within an area outlined by the interrupted lines. Any vertical-edge stimulus falling across this rectangle, regardless of its position, will excite some simple-field cells, leading to excitation of the higher-order cell.

C. BARRELS

Figure 15 from Woolsey & Van der Loos, 1970 as slightly modified by Simons & Land, 2003 which "shows a remarkable correspondence between the pattern of the mystacial vibrissae (whiskers) on the face of a mouse and the spatial organization of neuron clusters, 'barrels', in the contralateral cerebral cortex. http://simonslab.neurobio.pitt.edu/barrels/intro.htm	
a. Horizontal section through a barrel which, like columns, is normal to the cortical surface. The clusters of neurons by septa are quite evident.	b. Spatial distribution of mystacial vibrissae on the face of the mouse. Insert: sketch highlighting the organization.

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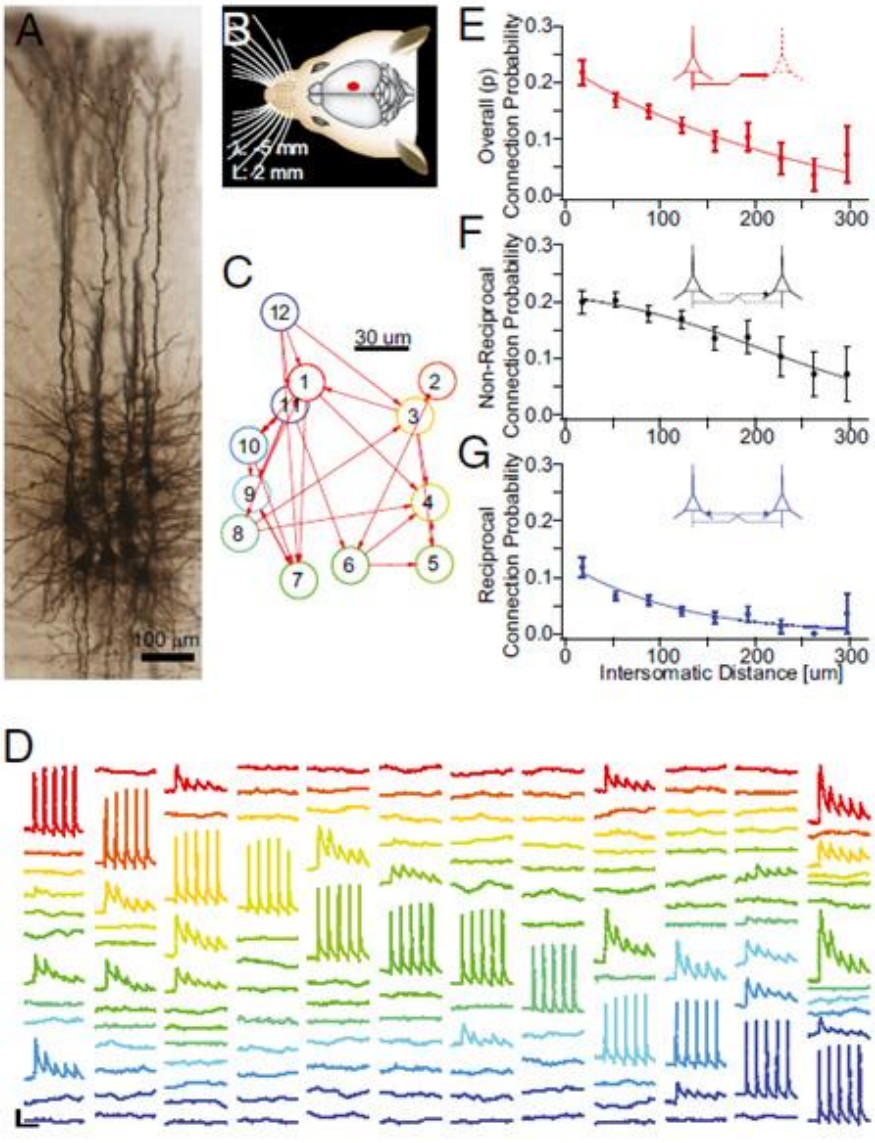
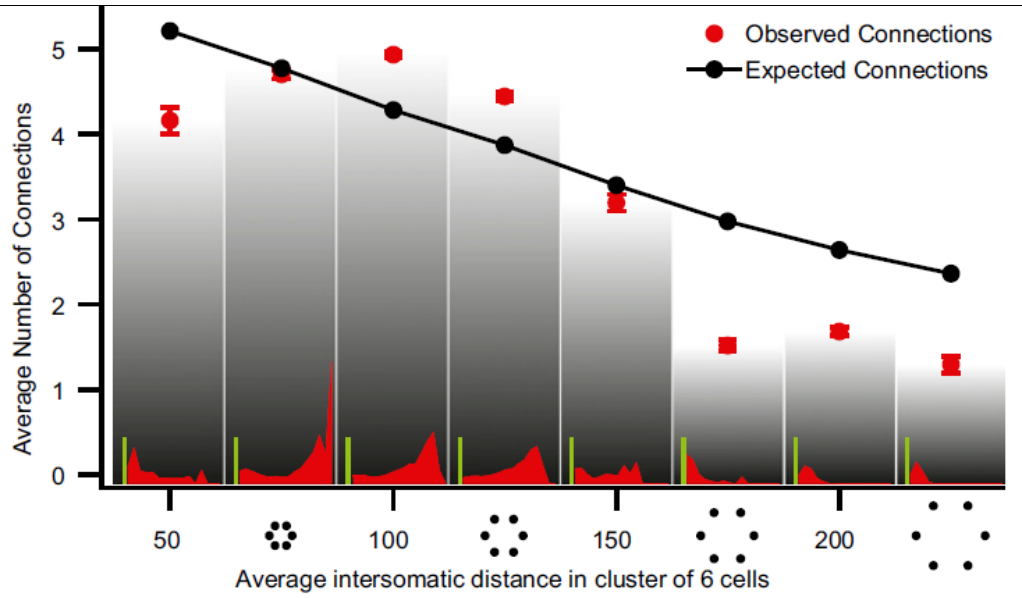
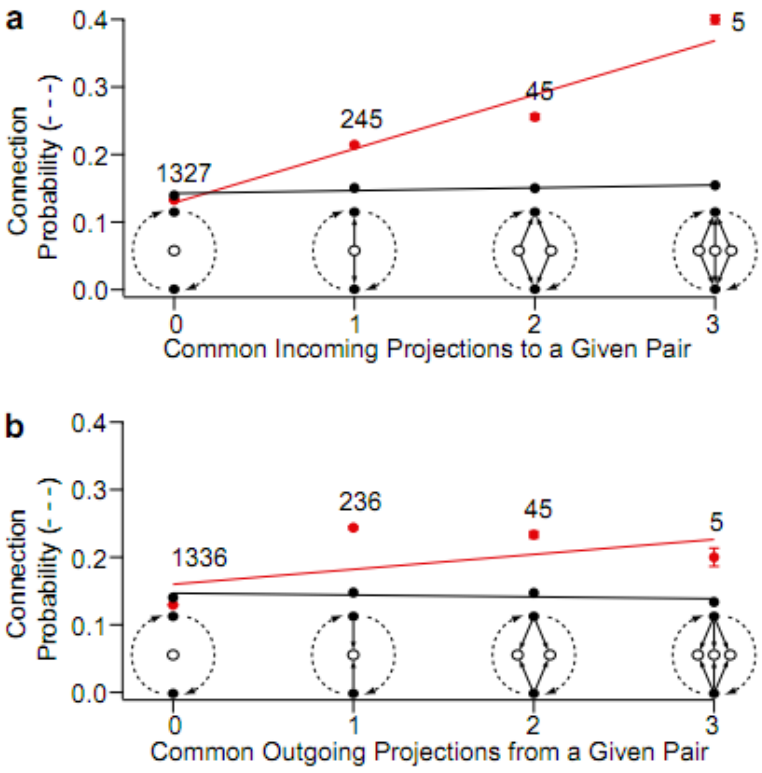


Fig. 1. Pair-wise connectivity. (A) Morphological staining of a cluster of 12 cells recorded simultaneously. (B) Region of the somatosensory cortex where recordings were carried out. Connectivity diagram of neurons in D. (D) Example of recorded traces in an experimental session. A different neuron is stimulated and the responses of the remaining neurons were recorded (displayed in columns). (E-G) Connection probability profiles as a function of distance. Error bars represent SEM. From Perin *et al.*, 2011, p. 2. The main diagonal of D shows all pair-wise stimulation and response. Large action potentials are from the cell being stimulated; responses are excitatory post-synamptic potentials (EPSPs). For example, column one shows cell 1 being stimulated and cells 7 and 10 responding, which are portrayed in C. B is probably adapted from Knott *et al*. (2002). [return to text]



From Perin *et al*. 2011, Figure 3, p. 3. Average number of connections in clusters of six cells as a function of cluster dimension. [return to text]



From Perin *et al*. 2011, Figure S4, p. 3. Common neighbor rule variations. (A) Effect on connection probability of different numbers of neurons simultaneously projecting to a pair of neurons. (B) Effect on connection probability of different numbers of neurons simultaneously receiving projections from a pair of neurons. Error bars show SEM. [return to text]

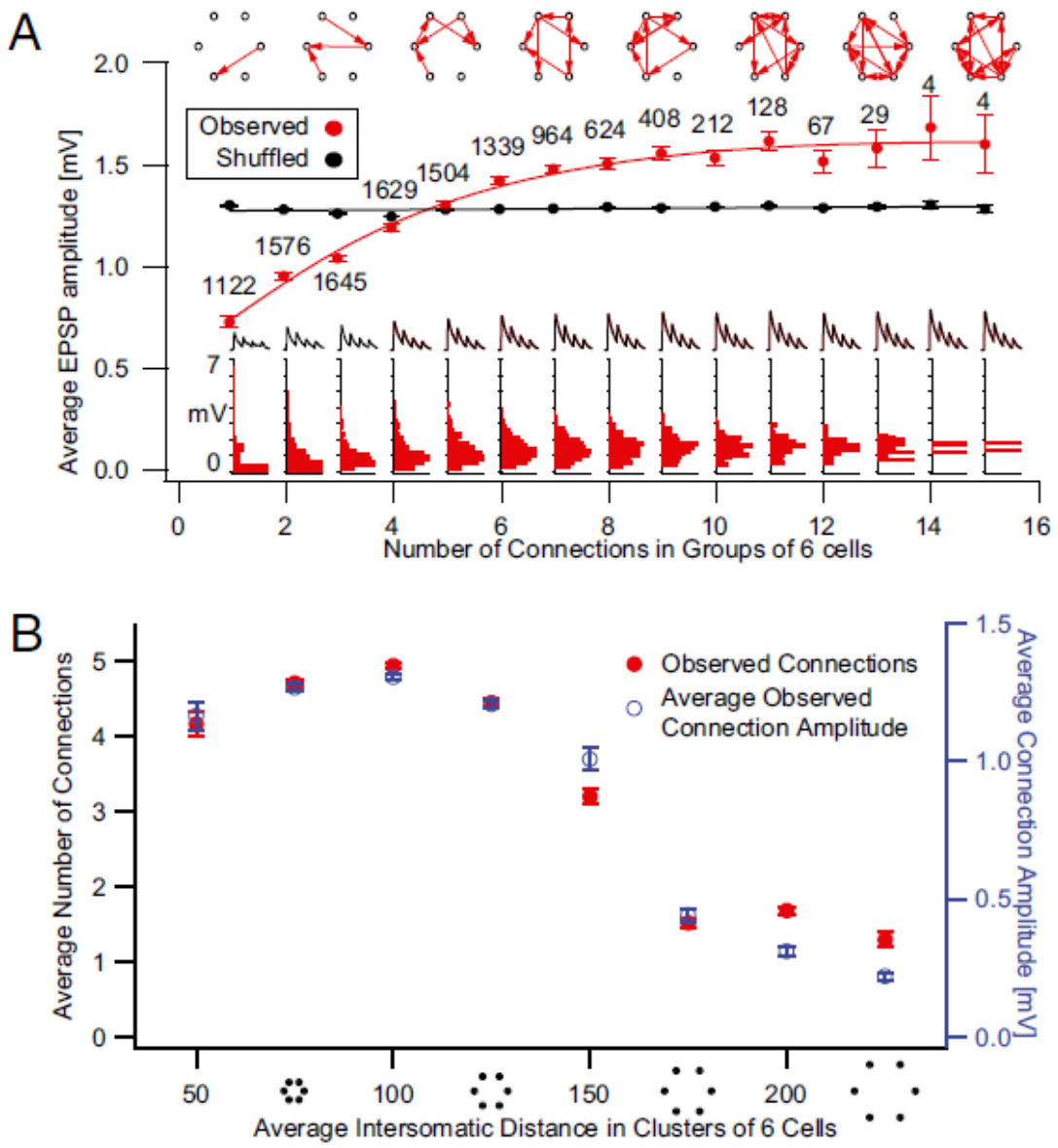


Fig. 6. Synaptic strengths Amplitudes. (*A*) Average EPSP amplitude as a function of number of connections in groups of six neurons (red) and results after random shuffling of connection amplitudes (black). (*Insets*) Distributions of average connection amplitude for groups with different numbers of connections. (*B*) Average number of connections in clusters of six cells grouped according to cluster spatial spread (red) and corresponding average connection amplitude (blue). Error bars represent SEM.

From Perin *et al*. 2011, Figure 6. Amplitudes as a function of number of connections and intersomatic distances in groups of six neurons within a microcircuit within a minicolumn. [return to text.]

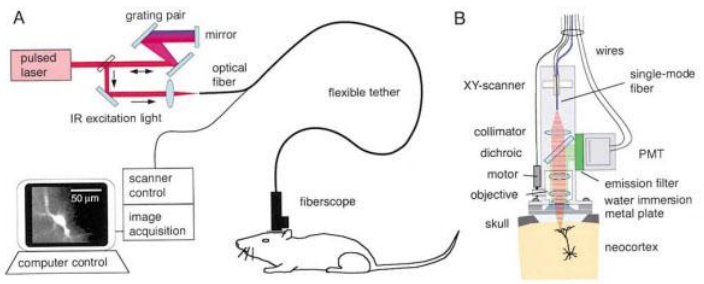


Figure 1. Two-Photon *In-vivo* Fiberscope Setup. From Helmchen *et al*. (2001).
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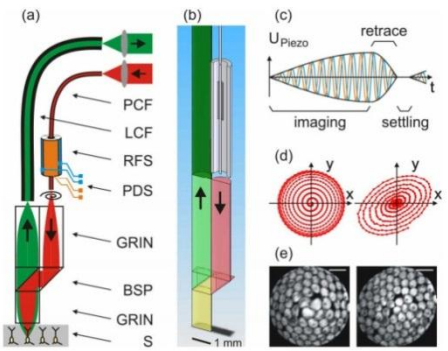

Fig. 1. Schematic (a) and perspective (b) representations of the ultra-compact fiber-optic two-photon microscope. From Engelbrecht *et al*. (2008).

D. HEBB

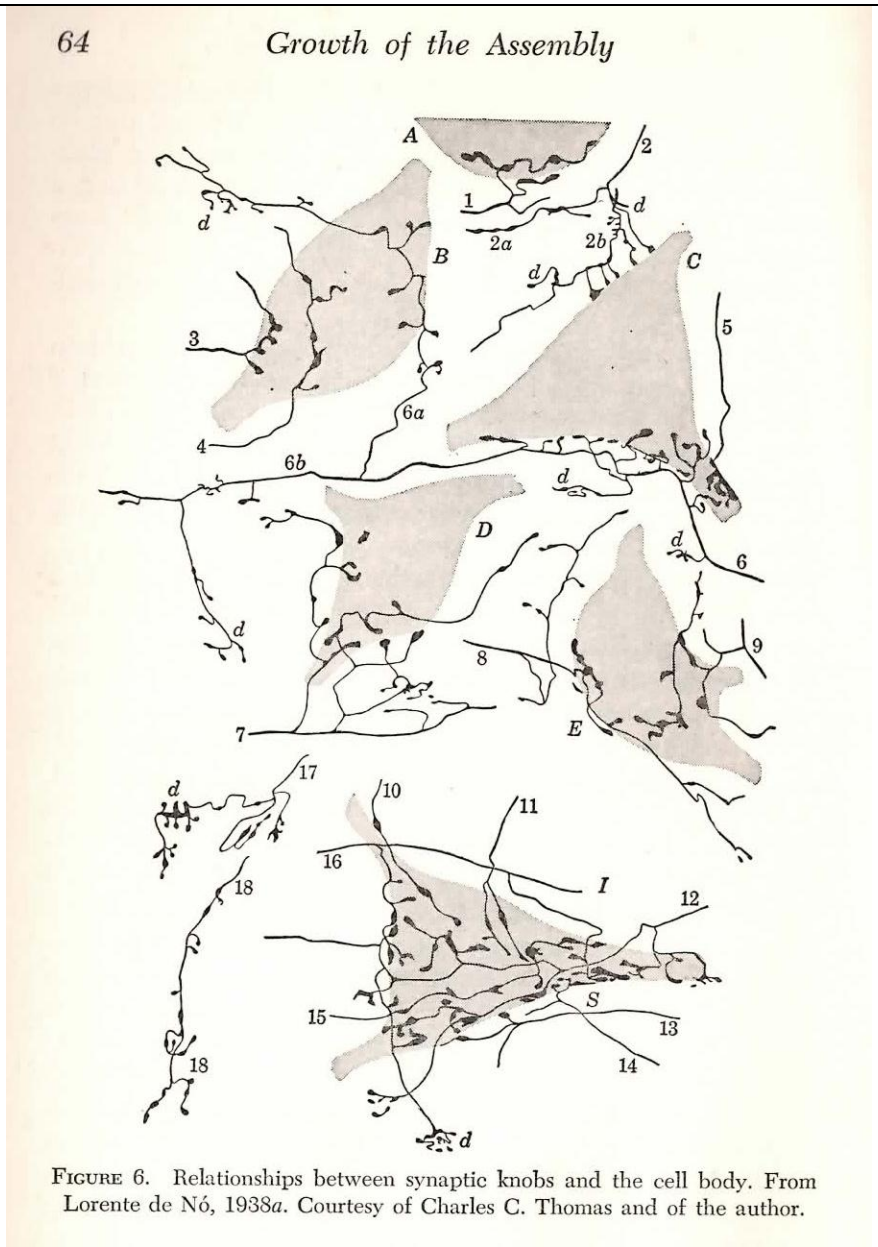

FIGURE 6. Relationships between synaptic knobs and the cell body. From Lorente de Nó, 1938*a*. Courtesy of Charles C. Thomas and of the author.

Hebb (1949, p. 64) shows cell bodies (shaded), and axons, their collatorals and boutons. Some collaterals extend from axons from a short distance between the main axon and the cell soma, some axons seem to bend from one trajectory to get closer to the cell body, some show a thickening as they pass in close contact with a cell body, and some make one or several direct paths to knobs on the cell bodies.

[return to Hebb Appendix 1C]

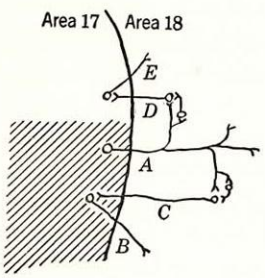

FIGURE 8

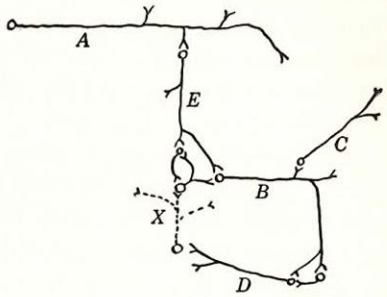

FIGURE 9

FIGURE 8. Cells *A* and *B* lie in a region of area 17 (shown by hatching) which is massively excited by an afferent stimulation. *C* is a cell in area 18 which leads back into 17. *E* is in area 17 but lies outside the region of activity. See text.

FIGURE 9. *A*, *B*, and *C* are cells in area 18 which are excited by converging fibers (not shown) leading from a specific pattern of activity in area 17. *D*, *E*, and *X* are, *among the many cells with which* A, B, *and* C *have connections*, ones which would contribute to an integration of their activity. See text.

Hebb (1949, p. 71) shows schematic networks of cell assemblies in visual cortical areas 17 (primary) and 18 (secondary). In figure 8, there is excitation from below onto cells in area 17 (shaded aea), which with repetition would tend for the synapses at A-> C and B->C to be repeatedly excited and experience growth. Figure 9 emphasizes the importance of convergence via a recurrent loop among other contributions to beginning an integration of a cell assembly though synaptic change.

[return to Hebb Appendix 1C]

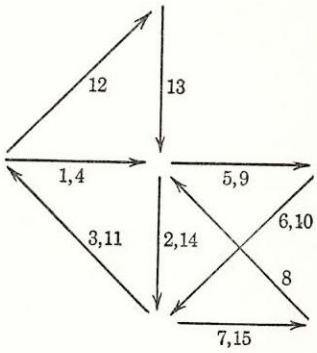

FIGURE 10. Arrows represent a simple "assembly" of neural pathways or open multiple chains firing according to the numbers on each (the pathway "1, 4" fires first and fourth, and so on), illustrating the possibility of an "alternating" reverberation which would not extinguish as readily as that in a simple closed circuit.