69. F. Briggs, E. M. Callaway, *J. Neurosci.* **21**, 3600 (2001).
70. E. M. Callaway, *Annu. Rev. Neurosci.* **21**, 47 (1998).
71. C. D. Gilbert, *J. Physiol.* **268**, 391 (1977).
72. Y. Yoshimura, J. L. Dantzker, E. M. Callaway, *Nature* **433**, 868 (2005).
73. G. M. Shepherd, A. Stepanyants, I. Bureau, D. Chklovskii, K. Svoboda, *Nat. Neurosci.* **8**, 782 (2005).
74. D. Feldmeyer, A. Roth, B. Sakmann, *J. Neurosci.* **25**, 3423 (2005).
75. J. Kozloski, F. Hamzei-Sichani, R. Yuste, *Science* **293**, 868 (2001).
76. F. Clasca, A. Angelucci, M. Sur, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 11145 (1995).
77. S. Song, P. J. Sjostrom, M. Reigl, S. Nelson, D. B. Chklovskii, *PLoS Biol.* **3**, e68 (2005).
78. V. Castellani, J. Bolz, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 7030 (1997).
79. F. Polleux, R. J. Giger, D. D. Ginty, A. L. Kolodkin, A. Ghosh, *Science* **282**, 1904 (1998).
80. F. Polleux, T. Morrow, A. Ghosh, *Nature* **404**, 567 (2000).
81. Y. Iwai *et al.*, *Mol. Cell. Neurosci.* **19**, 375 (2002).
82. K. Tabuchi, T. C. Sudhof, *Genomics* **79**, 849 (2002).
83. H. Cline, *Trends Neurosci.* **26**, 655 (2003).
84. G. G. Turrigiano, S. B. Nelson, *Nat. Rev. Neurosci.* **5**, 97 (2004).
85. N. B. Sawtell *et al.*, *Neuron* **38**, 977 (2003).
86. V. Dragoi, M. Sur, in *The Visual Neurosciences*, L. Chalupa, J. Werner, Eds. (MIT Press, Cambridge, MA, 2004), vol. 2, pp. 1654–1664.
87. M. C. Crair, J. C. Horton, A. Antonini, M. P. Stryker, *J. Comp. Neurol.* **430**, 235 (2001).
88. J. C. Crowley, L. C. Katz, *Science* **290**, 1321 (2000).
89. J. C. Crowley, L. C. Katz, *Nat. Neurosci.* **2**, 1125 (1999).
90. A. Antonini, M. P. Stryker, *Science* **260**, 1819 (1993).
91. T. N. Wiesel, D. H. Hubel, *J. Neurophysiol.* **28**, 1029 (1965).
92. C. J. Shatz, M. P. Stryker, *J. Physiol.* **281**, 267 (1978).
93. M. Fagiolini *et al.*, *Science* **303**, 1681 (2004).
94. T. K. Hensch, M. P. Stryker, *Science* **303**, 1678 (2004).
95. G. Liu, *Nat. Neurosci.* **7**, 373 (2004).
96. T. K. Hensch, *Annu. Rev. Neurosci.* **27**, 549 (2004).
97. N. S. Desai, R. H. Cudmore, S. B. Nelson, G. G. Turrigiano, *Nat. Neurosci.* **5**, 783 (2002).
98. H. Hering, M. Sheng, *Nat. Rev. Neurosci.* **2**, 880 (2001).
99. M. Maletic-Savatic, R. Malinow, K. Svoboda, *Science* **283**, 1923 (1999).
100. F. Engert, T. Bonhoeffer, *Nature* **399**, 66 (1999).
101. Q. Zhou, K. J. Homma, M. M. Poo, *Neuron* **44**, 749 (2004).
102. K. I. Okamoto, T. Nagai, A. Miyawaki, Y. Hayashi, *Nat. Neurosci.* **7**, 1104 (2004).
103. M. Matsuzaki, N. Honkura, G. C. Ellis-Davies, H. Kasai, *Nature* **429**, 761 (2004).
104. J. T. Trachtenberg *et al.*, *Nature* **420**, 788 (2002).
105. B. Lendvai, E. A. Stern, B. Chen, K. Svoboda, *Nature* **404**, 876 (2000).
106. A. Majewska, M. Sur, *Proc. Natl. Acad. Sci. U.S.A.* **100**, 16024 (2003).
107. S. Oray, A. Majewska, M. Sur, *Neuron* **44**, 1021 (2004).
108. J. T. Trachtenberg, M. P. Stryker, *J. Neurosci.* **21**, 3476 (2001).
109. J. T. Trachtenberg, C. Trepel, M. P. Stryker, *Science* **287**, 2029 (2000).
110. N. Mataga, Y. Mizuguchi, T. K. Hensch, *Neuron* **44**, 1031 (2004).
111. R. Lamprecht, J. LeDoux, *Nat. Rev. Neurosci.* **5**, 45 (2004).
112. N. Mataga, N. Nagai, T. K. Hensch, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 7717 (2002).
113. N. Berardi, T. Pizzorusso, G. M. Ratto, L. Maffei, *Trends Neurosci.* **26**, 369 (2003).
114. D. H. Hubel, T. N. Wiesel, *J. Physiol.* **195**, 215 (1968).
115. D. Ferster, K. D. Miller, *Annu. Rev. Neurosci.* **23**, 441 (2000).
116. D. C. Somers, S. B. Nelson, M. Sur, *J. Neurosci.* **15**, 5448 (1995).
117. J. Marino *et al.*, *Nat. Neurosci.* **8**, 194 (2005).
118. T. Bonhoeffer, A. Grinvald, *Nature* **353**, 429 (1991).
119. C. D. Gilbert, T. N. Wiesel, *J. Neurosci.* **9**, 2432 (1989).
120. T. N. Wiesel, D. H. Hubel, *J. Comp. Neurol.* **158**, 307 (1974).
121. B. Chapman, M. P. Stryker, *J. Neurosci.* **13**, 5251 (1993).
122. B. Chapman, I. Godecke, T. Bonhoeffer, *J. Neurobiol.* **41**, 18 (1999).
123. E. S. Ruthazer, M. P. Stryker, *J. Neurosci.* **16**, 7253 (1996).
124. E. M. Callaway, L. C. Katz, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 745 (1991).
125. L. E. White, D. M. Coppola, D. Fitzpatrick, *Nature* **411**, 1049 (2001).
126. D.-S. Kim, T. Bonhoeffer, *Nature* **370**, 370 (1994).
127. I. Godecke, T. Bonhoeffer, *Nature* **379**, 251 (1996).
128. H. Yu, B. J. Farley, D. Z. Jin, M. Sur, *Neuron* **47**, 267 (2005).
129. V. Dragoi, C. Rivadulla, M. Sur, *Nature* **411**, 80 (2001).
130. M. Sur, C. A. Leamey, *Nat. Rev. Neurosci.* **2**, 251 (2001).
131. F. Sengpiel, P. Stawinski, T. Bonhoeffer, *Nat. Neurosci.* **2**, 727 (1999).
132. M. Sur, in *Handbook of Multisensory Processes*, G. Calvert, C. Spence, B. E. Stein, Eds. (MIT Press, Cambridge, MA, 2004), pp. 681–694.
133. J. Sharma, A. Angelucci, M. Sur, *Nature* **404**, 841 (2000).
134. L. von Melchner, S. L. Pallas, M. Sur, *Nature* **404**, 871 (2000).
135. J. R. Newton, C. Ellsworth, T. Miyakawa, S. Tonegawa, M. Sur, *Nat. Neurosci.* **7**, 968 (2004).
136. T. Sun *et al.*, *Science* **308**, 1794 (2005).
137. O. V. Lagutin *et al.*, *Genes Dev.* **17**, 368 (2003).
138. J. Seoane, H. V. Le, L. Shen, S. A. Anderson, J. Massague, *Cell* **117**, 211 (2004).
139. E. M. Pera, A. Ikeda, E. Eivers, E. M. De Robertis, *Genes Dev.* **17**, 3023 (2003).
140. K. E. Hentges *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 13796 (2001).
141. Supported by grants from NIH, the Marcus Fund, and the Simons Foundation (M.S.); Nina Ireland Laboratory of Developmental Neurobiology, and the Hillblom Foundation, and a K05 award from NIMH (J.L.R.R.). We thank M. Brouillette and M. Potak for their help.

10.1126/science.1112070

REVIEW

Map Plasticity in Somatosensory Cortex

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Sensory maps in neocortex are adaptively altered to reflect recent experience and learning. In somatosensory cortex, distinct patterns of sensory use or disuse elicit multiple, functionally distinct forms of map plasticity. Diverse approaches—genetics, synaptic and in vivo physiology, optical imaging, and ultrastructural analysis—suggest a distributed model in which plasticity occurs at multiple sites in the cortical circuit with multiple cellular/synaptic mechanisms and multiple likely learning rules for plasticity. This view contrasts with the classical model in which the map plasticity reflects a single Hebbian process acting at a small set of cortical synapses.

A fundamental feature of neural circuits is the capacity for plasticity in response to experience or learning. A classic system for studying plasticity is primary somatosensory (S1) cortex. Somatosensory maps in S1 are highly plastic, both during development (*1*, *2*) and in adult animals (*3*). Plasticity occurs in response to peripheral lesions, passive sensory experience, and training on sensory tasks and is correlated with sensory perceptual learning. The underlying cellular mechanisms for map plasticity and its consequences for cortical processing are highly relevant to development, learning, and recovery of function after injury.

Rodent S1 cortex has emerged as a key model system in the analysis of the forms and mechanisms of map plasticity because of several experimental advantages. First, rodent S1 contains an orderly map of the large facial whiskers, which act as active tactile detectors, and large-scale map plasticity can be simply induced by trimming or plucking subsets of whiskers. Second, layer 4 (L4) of S1 contains an anatomical map of cell clusters, called "barrels," that is isomorphic to the arrangement of whiskers on the snout (*4*). Barrels can be visualized in brain slices, allowing cells and circuits at specific locations in the whisker map to be investigated in detail in vitro (*5*). Third, the superficial location of S1 allows live, optical imaging of neuronal function and structure, as well as whole-cell recording to study subthreshold events in vivo. Finally, molecular mechanisms of plasticity can be tackled using mouse genetics (*6*). Research on barrel cortex plasticity is particularly fascinating because of the wide range of techniques (*7*)—genetics, cell biology, in vitro and in vivo physiology, optical imaging—that are applied in the field. Here, we present an emerging consensus from these techniques that map plasticity is a distributed, multifaceted

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process with multiple synaptic and cellular mechanisms.

S1 Circuits and the Normal Whisker Map

A functional map of whisker receptive fields exists in S1, constructed by highly specific microcircuits whose anatomy and synaptic physiology are known in unprecedented detail. In the classical thalamocortical pathway (Fig. 1), afferents from the thalamic ventral posterior medial nucleus (VPM) innervate the L4 barrel corresponding to each whisker. Excitatory neurons in each barrel then project to L2/3 neurons in the same radial column. This feedforward intracolumnar pathway drives strong responses to each column's "principal whisker." Spread of excitation along cross-columnar pathways, together with broad tuning of thalamic inputs, confers weaker responses to neighboring, surround whiskers. Multiple types of inhibitory interneurons refine receptive fields and temporal response features. In a second afferent pathway, the septa between barrels in L4 receive less focused, multiwhisker input from the thalamic posterior medial nucleus. The result is a map in which each whisker activates a cortical region slightly larger than the anatomical column defined by its barrel (*8*) (Fig. 1). Synaptic connections between many identified cell classes have been quantitatively characterized (*8*–*11*), which suggests that, within the foreseeable future, it will be possible to identify cell type–specific synaptic weight and connectivity changes underlying S1 map plasticity.

Development of the Barrel Map

Both genes and neural activity instruct development of S1 maps. Signaling molecules partition the early cortex into specific subdivisions (*12*), as demonstrated by the duplication of the barrel field after electroporation of the signaling molecule fibroblast growth factor 8 (FGF-8) (*13*). Thus, thalamic afferents recognize gradients of signaling molecules in an early and intrinsically specified somatosensory cortex (*13*), rather than instructing a tabula rasa–like cortical sheet. Barrel formation within the prespecified S1 is instructed by peripheral afferents (*1*) and involves multiple, activity-dependent processes. These processes have begun to be revealed by genetic approaches [for review, see (*14*)].

Forms of Map Plasticity in S1

Sensory manipulations alter S1 maps. Multiple, distinct forms of map plasticity are seen depending on the pattern of sensory input, behavioral context, and age. Two basic principles generally hold. First, whisker manipulations early in life (the first postnatal week) cause rapid map plasticity in L4, consistent with plasticity at thalamocortical synapses (*6*). In older animals, however, plasticity tends to occur first in L2/3 and L5, and only later or not at all in L4 (*15*–*18*), although exceptions can occur (*19*). This suggests that L4 thalamocortical synapses exhibit an early critical period for rapid plasticity, whereas intracortical synapses in other layers remain highly plastic and are the primary places where rapid plasticity occurs throughout life. Second, changes in whisker use or activity drive plasticity of the whisker receptive field map, but only lesions of primary afferents disrupt anatomical patterning of barrels and only in neonates (*1*). Thus, use-dependent and lesion-dependent plasticity are mechanistically distinct (*6*, *14*).

Hebbian plasticity in response to preferential whisker use or training. In the classical form of map plasticity as originally defined in visual cortex, differential use of two sensory inputs causes the representation of the overused input to expand and that of the underused input to shrink. This is termed Hebbian plasticity because it follows Hebbian synaptic plasticity rules (*20*) and is commonly hypothesized to increase the cortical processing capacity of behaviorally relevant inputs. Hebbian plasticity occurs in nonwhisker S1 in response to overuse or preferential training of small regions of the hand or paw (*3*) and in whisker S1 in response to trimming or removing a subset of whiskers, which increases the behavioral salience of spared whiskers (*6*, *15*, *16*, *21*), or by appetitive or aversive conditioning of specific whiskers (*22*). The result is that spared or trained inputs expand in the S1 map, and deprived or untrained inputs shrink (Fig. 2).

Components of Hebbian plasticity. Hebbian plasticity in S1 has two

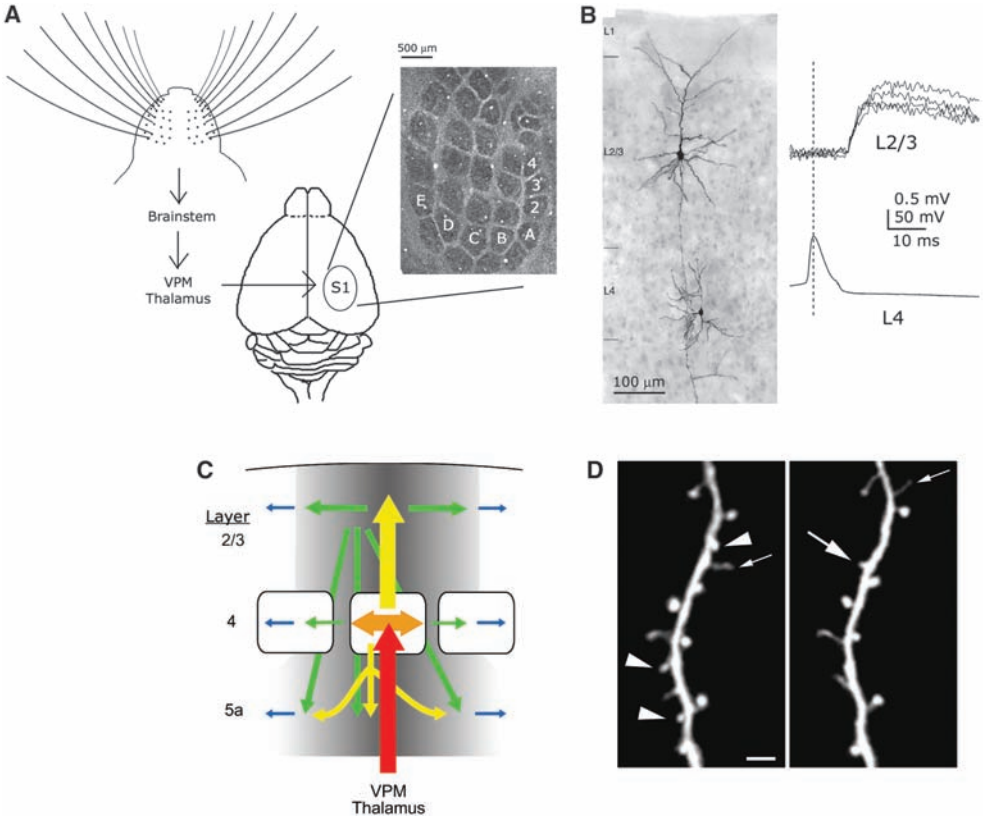

Fig. 1. Functional circuits in S1 cortex. (**A**) Pathway from whiskers to S1. (Inset) Cytochrome oxidase–stained barrels in layer 4 of S1. Letters and numbers indicate whisker rows and arcs. (**B**) Schematic flow of excitation evoked by single whisker deflection. Only the VPM input to cortex is considered. Order of events progresses from red to yellow to green to purple. Response strength is denoted by arrow thickness (*6*). Gray, cortical area with strong or moderate spiking responses to the whisker. (**C**) Example of characterization of synaptic physiology in S1, for a unitary connection from an L4 spiny stellate cell to a simultaneously recorded L2/3 pyramidal cell (*11*). Traces show excitatory postsynaptic potentials (EPSPs) (top right) evoked by single action potentials the L4 cell (bottom right). (**D**) Dynamic dendritic spines revealed by long-term in vivo two-photon imaging in S1 of an adolescent (1-month-old) rat [from (*82*)]. (Left) Apical dendritic segment from a layer 5 pyramidal cell. (Right) The same dendritic segment 2 weeks later. Arrowheads and arrows show spine elimination and formation. Thin arrows mark dynamic filopodia. Scale bar, 2 μm.

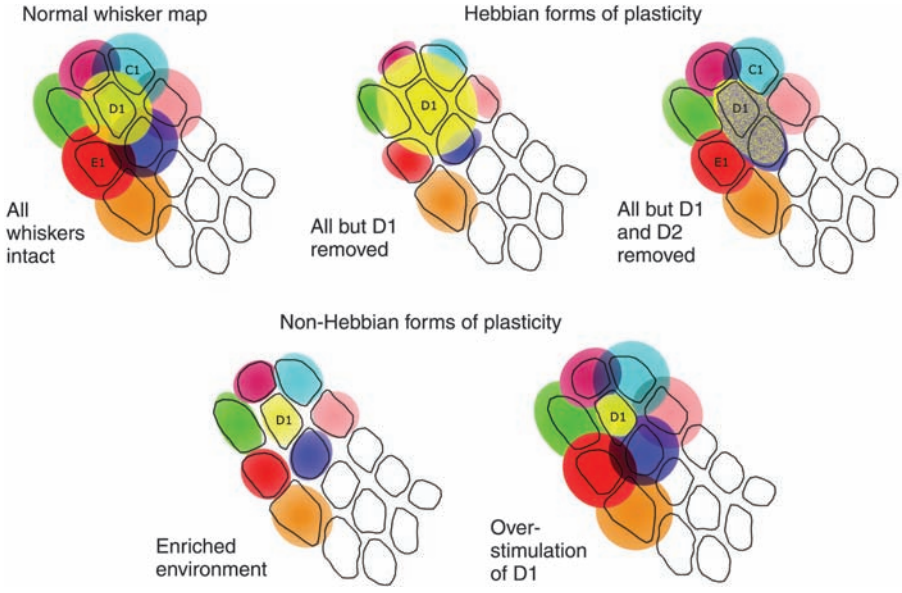

Fig. 2. Forms of whisker map plasticity in S1 cortex. In these schematized functional whisker maps in L2/3 of S1, colored regions represent cortical areas responding to different whiskers, with color saturation coding response strength. In normal rats, each whisker activates a cortical area slightly larger than the cortical column defined by its L4 barrel (barrels outlines are shown in black) (*8*). Removing all but the D1 whisker in adolescent rats causes Hebbian expansion of the spared, D1 whisker and weakening of deprived, surrounding whiskers within the map (*6*). Removing all but D1 and D2 whiskers causes D1 and D2 to merge within the map but not to expand into deprived columns (*16*). In two non-Hebbian forms of map plasticity, exposure to a novel, naturalistic environment sharpens the whisker map and weakens whisker responses (*18*), and overstimulation of a single whisker causes that whisker to shrink within the map.

separable components, which implies two mechanistically distinct processes for plasticity. In the first component, whisker deprivation selectively weakens neural responses to deprived whiskers, causing deprived whisker representations to shrink (*15*, *21*, *23*). Weakening is an active process that requires cortical spiking and is partly driven by competition from spared neighboring whiskers. One cellular basis for this component of plasticity is deprivation-induced weakening of the L4 to L2/3 (L4-L2/3) excitatory projection (*15*), which has been directly observed in S1 slices from whisker-deprived rats (*24*, *25*).

In a second, developmentally and genetically independent (*6*, *26*) component of Hebbian plasticity, responses to spared whiskers become enhanced (*15*, *21*, *27*, *28*). When isolated whiskers are spared, enhancement of spared whisker responses occurs in surrounding deprived columns, causing the spared whisker representation to expand in the S1 map (*15*, *21*, *27*). When multiple neighboring whiskers are spared, enhancement occurs instead in neighboring spared columns, which causes the representations of individual spared whiskers to merge or overlap (*16*) (Fig. 2). The latter case exemplifies classical Hebbian strengthening of coactive inputs onto common targets (''Neurons that fire together wire together''), which is a robust feature of map plasticity (*29*). Both cases may reflect enhanced transmission on excitatory, cross-columnar pathways into deprived or spared columns (*6*, *30*).

Deprivation of all whiskers degrades map topography. Trimming all whiskers during a narrow critical period at the peak of L2/3 synaptic development causes L2/3 neurons to adopt broad, unfocused receptive fields and a disordered whisker map, while the L4 map remains normal (*17*). This degraded map topography reflects increased cross-columnar (relative to within-column) input to L2/3 neurons (*31*) and disruption of normal barrel-septal segregation within the L4-L2/3 projection such that L2/3 neurons receive abnormally strong input from L4 septa, which have broad, poorly ordered fields (*25*). This suggests that developing barrel and septal inputs may compete for L2/3 targets, with experience driving normal segregation of these pathways.

Decreased representation of overstimulated whiskers. Several forms of plasticity cannot be explained by Hebbian or activity-based competitive mechanisms. Sustained, 24-hour passive stimulation of a whisker causes the representation of the activated whisker to weaken and to shrink in adult S1 (*32*). This plasticity occurs in L4 and is correlated with an increase in number and density of GABAergic synapses onto L4 spines (*19*). This effect may represent a homeostatic mechanism to normalize firing rates and/or a habituation process to reduce responses to repeated, behaviorally insignificant input.

Regulation of map precision and signs of plasticity by sensory enrichment. Transferring adult rats from familiar home cages into complex natural environments causes another non-Hebbian form of plasticity in which whisker representations contract in L2/3, thus sharpening the whisker map (Fig. 2). L4 receptive fields are unaffected (*18*). Similar map sharpening occurs rapidly during acute arousal and exploration (*33*). One possible mechanism is that environmental novelty upregulates arousal-related modulators, which are known to act in cortex to shrink whisker representations (*33*). Exposure to a novel environment for only a few minutes per week, which is not enough to sharpen the whisker map, also has the profound and unexplained effect of reversing the sign of Hebbian plasticity: When all but one whisker are removed, the representation of the spared whisker shrinks, rather than expands (*34*). The existence of these functionally distinct forms of plasticity indicates that multiple cellular plasticity mechanisms and learning rules act in S1, beyond canonical Hebbian plasticity mechanisms.

Physiological Mechanisms of Plasticity

Substantial progress has been made in S1 in identifying the underlying cellular mechanisms for Hebbian and other forms of map plasticity. In classical models, rapid components of Hebbian plasticity reflect long-term potentiation (LTP) and depression (LTD) at cortical synapses; slower components reflect anatomical rearrangement of cortical microcircuits (*3*). Competition between inputs, which is often associated with Hebbian map plasticity, is not directly predicted from Hebbian synaptic plasticity rules and may require an additional cellular mechanism (*35*, *36*). S1 experiments support certain aspects of this model (e.g., involvement of LTP and LTD in Hebbian plasticity), but refute others (e.g., that anatomical plasticity must be slow to occur). Mechanisms for non-Hebbian forms of plasticity are also emerging (*19*, *36*).

LTP and LTD. Many S1 synapses exhibit *N*-methyl-D-aspartate (NMDA) receptor-dependent LTP and LTD, and the capacity for LTP and LTD correlates with critical periods for map plasticity in each layer (*37*). Pharmacological blockade or transgenic deletion of cortical NMDA receptors impairs barrel development (*14*) and refinement and plasticity of receptive fields (*38*–*40*). During Hebbian map plasticity, the enhancement of spared whisker responses is abolished or impaired in mice lacking functional α-CaMKII (calcium/calmodulin-dependent protein kinase II, type α) or α/δ CREB [cyclic adenosine monophosphate (cAMP) response element–binding protein], or expressing autophosphorylation-incompetent α-CaMKII, all of which are required for cortical LTP (*6*). Thus, LTP [or CaMKII/CREB-

dependent structural rearrangements related to LTP (*41*)] is a likely substrate for this component of plasticity. The synaptic locus for LTP may be excitatory pathways from spared to neighboring columns, potentiation of which would expand the spared whisker representation.

LTD, or an LTD-like synaptic weakening, appears to be a major substrate for the shrinkage of deprived whisker representations during Hebbian map plasticity. Weakening of the excitatory L4-L2/3 projection has been detected physiologically after partial whisker deprivation, in ex vivo S1 slices prepared from whisker-deprived rats (*24*, *25*). This weakening occurs without loss of L4 neurons, axonal boutons, or changes in postsynaptic excitability (*24*, *42*, *43*). Instead, deprivation-induced weakening occludes LTD and shares apparent presynaptic expression with LTD, which suggests that it represents LTD induced in vivo (*24*, *44*). Whether this reflects physiological weakening of preexisting synapses, synapse elimination, or both, is unknown. Conversely, normal whisker use drives measurable LTP at L4-L2/3 synapses (*45*), which indicates that L4-L2/3 synapses are a site of bidirectional, experience-dependent plasticity in S1.

Other physiological mechanisms of plasticity. LTP and LTD at excitatory synapses are not the only mechanisms for cortical plasticity. Short-term synaptic dynamics are altered by sensory experience (*5*). Inhibitory circuits are also altered: Levels of γ-aminobutyric acid (GABA), GABA type A α1 receptors, and the GABA-synthesizing enzyme GAD67 (glutamic acid decarboxylase) are regulated by sensory deprivation and sensory learning, and the number and density of GABA synapses in L4 are decreased by whisker deprivation and increased by passive stimulation (*46*). In addition, an apparently large number of barrel cortex neurons exhibit very low firing rates (*47*); recruitment of these silent neurons into the active neuronal population could be an important plasticity mechanism (*48*). The diversity of plasticity mechanisms identified in the few existing studies suggests that additional mechanisms remain to be discovered.

Learning Rules for Plasticity

The quantitative relationship between pre- and postsynaptic activity parameters and resulting synaptic plasticity is termed the synaptic learning rule. A central dogma is that experience drives plasticity via local, sensory-evoked activity patterns that engage these learning rules (*20*). A major focus of research is to determine the relevant learning rules and network activity patterns that drive plasticity in vivo. Best studied are learning rules for LTP and LTD, which include rate-dependent rules in which high- and low-frequency presynaptic firing, respectively, drive LTP and LTD, and spike timing-dependent plasticity (STDP) rules in which changes in millisecond-scale timing of pre- and postsynaptic spikes drive LTP and LTD largely independent of firing rate (*49*).

STDP and Hebbian synaptic plasticity. The relevant learning rule for plasticity has been studied for deprivation-induced LTD at L4-L2/3 synapses, which contributes to Hebbian weakening of deprived whisker representations. L4-L2/3 synapses exhibit both rate-dependent plasticity and STDP in vitro (*24*, *50*). In STDP at this synapse, LTP is induced when the L4 cell fires 0 to 15 ms before L2/3 cells, and LTD is induced when firing order is reversed, for spiking delays of 0 to 50 ms (*50*). STDP learning rules biased toward LTD are common for cortical pyramidal cells, inherently drive Hebbian plasticity, and predict LTD in response to either reliable, postleading-prefiring or to uncorrelated spiking (*50*). In vivo firing patterns suggest that STDP is the relevant learning rule by which whisker deprivation drives LTD: When all whiskers are deflected together to mimic normal whisking in anesthetized animals, L4 neurons spike reliably before L2/3 neurons. However, when all whiskers except the principal whisker are deflected to mimic acute whisker deprivation, L4-L2/3 firing decorrelates and mean firing order reverses. These spike timing changes are quantitatively appropriate to predict spike timing–dependent LTD (*51*). In contrast, acute deprivation changes mean firing rate only modestly and insufficiently to predict rate-dependent LTD (*51*). Thus, spike timing, not spike rate, may be the key parameter that drives synaptic weakening during Hebbian plasticity in S1.

Neuromodulation. Hebbian plasticity is enhanced by behavioral relevance and attention, particularly in adults. Attentional gating of plasticity may be provided by neuromodulators such as acetylcholine (ACh) released in cortex by basal forebrain inputs. Map plasticity in S1 and other areas requires ACh, and pairing of whisker stimuli with ACh application drives receptive field plasticity (*52*). This suggests that ACh and other modulators may fundamentally gate or modify Hebbian learning rules during appropriate behavioral contexts.

Competition between inputs. Competition between spared and deprived inputs drives key aspects of S1 plasticity (*6*), but the biological mechanisms and learning rules for competition are almost entirely unknown. In one proposed mechanism, Hebbian learning rules themselves change as a function of postsynaptic activity, so that depriving one set of inputs increases the likelihood that remaining, spared inputs will strengthen (*35*). STDP provides an alternative explanation for competition, because multiple inputs actively compete in STDP models for control of spike timing. Competition could also be implemented by non-Hebbian, homeostatic forms of plasticity (*36*), or by anatomical competition for synaptic space by dynamic axons and dendrites. However, the actual mechanisms of competition in vivo remain unknown.

Structural Changes

In the last few years, classical structural analysis of cortical circuits based on static, postmortem tissue has been revolutionized by the study of dynamic, living neurons expressing fluorescent proteins (*53*) and visualized in vivo by two-photon imaging (*54*, *55*). This technique has revealed that cortical circuits are structurally highly dynamic and are regulated by sensory experience (Fig. 1D; Fig. 3). Accordingly, even rapid components of cortical map plasticity could be mediated, in part, by structural changes in cortical microcircuits (*56*), and physiological changes in synapse strength may be closely linked to structural plasticity (*57*–*59*).

Dendritic branch dynamics. Early in life, dendritic branches are highly dynamic, and dendritic architecture is altered in response to whisker trimming (*60*), environmental enrichment (*61*), and peripheral lesion (*1*). In adults, basic dendritic branch structure in S1 is highly stable over weeks of normal sensory experience (*62*, *63*), and branching is unaffected by whisker trimming or plucking (*62*), although older studies suggest that complex environments can increase dendritic complexity (*64*). Peripheral lesions continue to drive robust dendritic branch plasticity in adults (*65*). In line with in vitro evidence (*66*), one might speculate that neurotrophic factors—or the lack thereof—trigger dendritic remodeling in response to lesions. Thus, structural changes in dendritic branches may contribute to developmental and lesion-induced plasticity but are unlikely to contribute to experience-dependent plasticity in mature animals.

Axonal dynamics. Cortical axonal trees are more difficult to visualize, and consequently, we have only limited information about cortical axonal dynamics in vivo. In visual cortex, there is massive, experience-dependent axonal remodeling during development (*67*), but it is not clear to what extent such axonal remodeling occurs in barrel cortex. Initial outgrowth of L4 axons into L2/3 during barrel cortex development is largely topographically specific (*68*) and is not affected by whisker plucking (*42*). While alterations of afferent input can alter axonal fields in adult visual cortex (*69*), the stability of the large-scale organization of the axonal network in the adult barrel cortex remains to be investigated (*56*).

Spine dynamics. Dendritic spines (*70*) are important biochemical compartments in cortical processing, and spine motility and turnover have been the focus of numerous in vivo imaging studies (*62*, *63*, *71*, *72*). These studies indicate that spines can be highly dynamic structures, with dynamics regulated by senso-

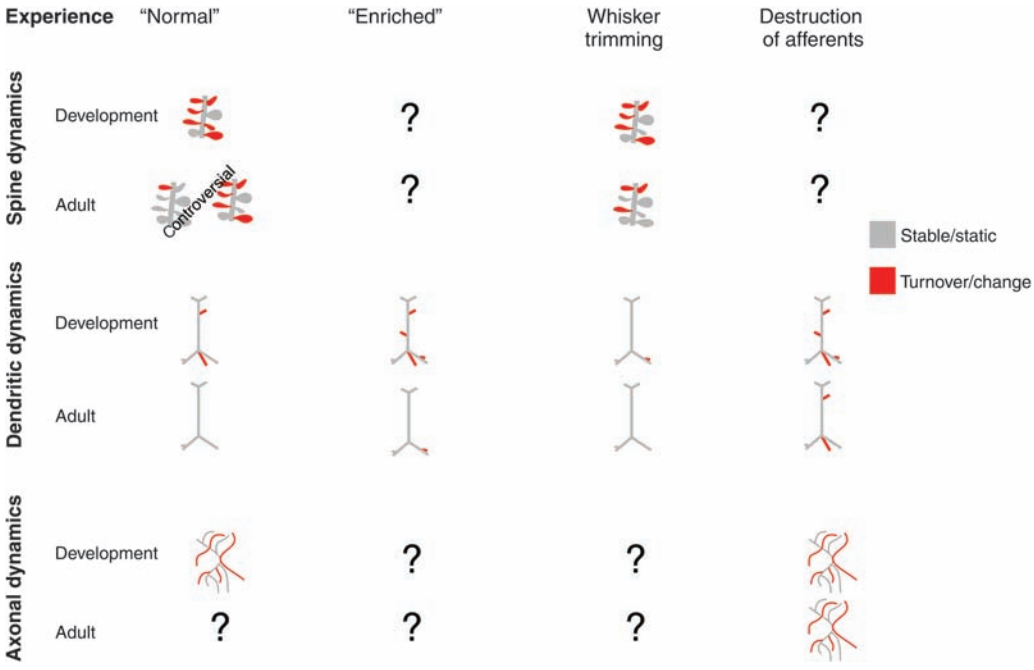

Fig. 3. Experience induced structural changes in S1 cortex. Schematic representation of experience- and deprivation-induced alterations in barrel cortex circuitry. Spine data refer to chronic in vivo imaging experiments (*62*, *63*, *71*, *72*). Dendritic data were collected in chronic in vivo imaging experiments (*11*, *64*) or in conventional anatomical experiments (*1*, *18*, *60*, *61*, *64*). The effects of sensory enrichment include data from non-S1, as well as S1, barrel cortex.

ry experience. Although there are some quantitative disagreements, these studies agree on a number of basic facts: (i) Spines are dynamically added and eliminated in vivo over a time course of hours (spine turnover). (ii) Turnover decreases with age. (iii) Spines are heterogeneous and differ in their turnover rates. (iv) Thick bulbous spines have lower turnover rates than thin spines. (v) There is a net loss of spines in late postnatal development.

In the developing brain there is massive motility of filopodia and high turnover rates of spines, and spine dynamics are regulated by experience (*55*, *62*). Using in vivo two-photon imaging and subsequent electron microscopic reconstruction of imaged spines, it was shown that many dendritic protrusions in S1 carry synapses, but that synapses are probably absent from sites of recently retracted spines, which suggests that spine sprouting and retraction are associated with synapse formation and elimination (*62*). Conclusive proof of this important point may be obtained in the future by imaging markers for synaptic structures [e.g., AMPA receptors (*73*)]. Such approaches, which can also be applied to presynaptic structures, will also take the field from imaging what we can see best (anatomical protrusions on dendrites) toward what we are interested in most (functional synaptic connections). In the adult brain, spines are more stable, but details remain controversial. Authors agree that large thick spines are more stable than thin spines (*63*, *71*, *72*), but disagree whether 75% (*71*) or 95% (*63*, *72*) of spines are stable over weeks in the adult brain. Complicating these findings is disagreement on the classification of spines versus other dendritic protrusions. Thus, it is unclear if what one group (*63*, *72*) considers a filopodium [a long, thin protrusion lacking a bulbous head (*72*)], is considered a thin spine by another group (*62*, *71*, *73*). Post hoc ultrastructural analysis by electron microscopy (EM) will help resolve this issue. Further scrutiny of experimental details like brain exposure, pharmacological treatments, animal strain, and housing conditions is required to compare spine turnover across groups and to determine its role in cortical plasticity.

Several important future directions are obvious in the analysis of structural plasticity of barrel cortex. The first is to devise strategies to independently analyze structural dynamics of identified cell types within specific intracortical circuits. A second issue is the origin of wiring specificity. Pairs of neighboring excitatory barrel cortex neurons are either unconnected or share four or five synaptic terminals (*9*, *10*, *74*). This scenario is dramatically different from what is expected for a probabilistic connectivity, which—based on axonal and dendritic geometries—predicts neighboring cortical neurons to be connected usually by one terminal, rarely by two, and almost never by three terminals or more (*75*). The origin of such precise wiring, whether activity-dependent processes and/or genetic cues, is entirely unclear.

A third major issue is to understand how structural plasticity is related to functional changes in synaptic efficacy like LTP and LTD. In vitro, late phases of LTP and LTD are correlated with synapse and spine formation and elimination (*57*, *58*). Thus, activity may rapidly regulate synaptic efficacy by LTP and LTD, which in turn may modulate structural dynamics and lead to long-term effects on morphology of axons and/or dendrites (*59*). When examined, most vertebrate studies in vivo report parallel changes in synaptic structure and function, but the alternate possibility that structural and functional plasticity are controlled independently via dissociable signaling pathways, as reported in invertebrates (*76*), cannot be ruled out at present.

Outlook and Summary

Ramón y Cajal once pointed out that the cortex is a very difficult matter, a tissue of endless complications, where any kind of simplistic approach is bound to fail (*77*). A strength of the work on S1 plasticity has been to avoid such simplification. S1 map plasticity is not a unitary phenomenon but has many distinct forms with multiple components, cellular mechanisms, and sites of plasticity. Similar complexity is likely to exist in other cortical areas.

Where do we go from here? Some of the most promising approaches lie in the combination of novel genetic, optical, and physiological techniques. Recent improvements in gene transfer methods allow sparse transfection and genetic alteration of cells in an otherwise intact brain (*78*, *79*). Transfected cells can then be electrophysiologically analyzed by two-photon targeted patch recordings in vivo (*80*) in order to detect effects on development and plasticity of sensory responses. The tremendous spatiotemporal specificity of such manipulations will help determine how genes or single-cell activity patterns contribute to systems-level properties like plasticity.

A second challenge is to identify additional synaptic learning rules that drive plasticity in vivo. Here, one obvious approach is to utilize recent advances in multisite recording techniques to characterize the network activity patterns that occur naturally in vivo to drive map plasticity. A third challenge is to develop the computational tools and theoretical framework necessary to understand how the multiple discrete mechanisms and sites of plasticity, including both functional and structural changes, work together in cortical circuits to produce overall map plasticity. Finally, future research must address the behavioral and perceptual consequences of barrel cor-

tex plasticity, which are—with few exceptions (*81*)—poorly understood. Although complex, a mechanistic, cellular-level explanation of S1 map plasticity appears increasingly tractable and would constitute a major step toward understanding cortical information storage.

References and Notes

1. H. Van der Loos, T. A. Woolsey, *Science* **179**, 395 (1973).
2. D. J. Simons, P. W. Land, *Nature* **326**, 694 (1987).
3. D. V. Buonomano, M. M. Merzenich, *Annu. Rev. Neurosci.* **21**, 149 (1998).
4. T. A. Woolsey, H. Van der Loos, *Brain Res.* **17**, 205 (1970).
5. G. T. Finnerty, L. S. Roberts, B. W. Connors, *Nature* **400**, 367 (1999).
6. K. Fox, *Neuroscience* **111**, 799 (2002).
7. M. Brecht *et al.*, *J. Neurosci.* **24**, 9223 (2004).
8. C. C. Petersen, *Pflugers Arch.* **447**, 126 (2003).
9. D. Feldmeyer, V. Egger, J. Lubke, B. Sakmann, *J. Physiol.* **521**, 169 (1999).
10. R. A. Silver, J. Lubke, B. Sakmann, D. Feldmeyer, *Science* **302**, 1981 (2003).
11. D. Feldmeyer, J. Lubke, R. A. Silver, B. Sakmann, *J. Physiol.* **538**, 803 (2002).
12. T. Shimogori, V. Banuchi, H. Y. Ng, J. B. Strauss, E. A. Grove, *Development* **131**, 5639 (2004).
13. T. Fukuchi-Shimogori, E. A. Grove, *Science* **294**, 1071 (2001).
14. R. S. Erzurumlu, P. C. Kind, *Trends Neurosci.* **24**, 589 (2001).
15. S. Glazewski, K. Fox, *J. Neurophysiol.* **75**, 1714 (1996).
16. M. E. Diamond, W. Huang, F. F. Ebner, *Science* **265**, 1885 (1994).
17. E. A. Stern, M. Maravall, K. Svoboda, *Neuron* **31**, 305 (2001).
18. D. B. Polley, E. Kvasnak, R. D. Frostig, *Nature* **429**, 67 (2004).
19. G. W. Knott, C. Quairiaux, C. Genoud, E. Welker, *Neuron* **34**, 265 (2002).
20. D. O. Hebb, *Organization of Behavior* (Wiley, New York, 1949).
21. H. Wallace, K. Fox, *J. Neurobiol.* **41**, 58 (1999).
22. E. Siucinska, M. Kossut, *Cereb. Cortex* **6**, 506 (1996).
23. A. Skibinska, S. Glazewski, K. Fox, M. Kossut, *Exp. Brain Res.* **132**, 134 (2000).
24. C. B. Allen, T. Celikel, D. E. Feldman, *Nat. Neurosci.* **6**, 291 (2003).
25. G. M. Shepherd, T. A. Pologruto, K. Svoboda, *Neuron* **38**, 277 (2003).
26. S. Glazewski, K. P. Giese, A. Silva, K. Fox, *Nat. Neurosci.* **3**, 911 (2000).
27. M. Kossut, *Exp. Brain Res.* **123**, 110 (1998).
28. D. L. Maier, G. M. Grieb, D. J. Stelzner, J. S. McCasland, *Exp. Neurol.* **184**, 737 (2003).
29. X. Wang, M. M. Merzenich, K. Sameshima, W. M. Jenkins, *Nature* **378**, 71 (1995).
30. M. A. Lebedev, G. Mirabella, I. Erchova, M. E. Diamond, *Cereb. Cortex* **10**, 23 (2000).
31. A. Schierloh, M. Eder, W. Zieglgansberger, H. U. Dodt, *Eur. J. Neurosci.* **20**, 1118 (2004).
32. E. Welker, S. B. Rao, J. Dorfl, P. Melzer, H. van der Loos, *J. Neurosci.* **12**, 153 (1992).
33. M. A. Castro-Alamancos, *Prog. Neurobiol.* **74**, 213 (2004).
34. D. B. Polley, C. H. Chen-Bee, R. D. Frostig, *Neuron* **24**, 623 (1999).
35. E. L. Bienenstock, L. N. Cooper, P. W. Munro, *J. Neurosci.* **2**, 32 (1982).
36. G. G. Turrigiano, S. B. Nelson, *Curr. Opin. Neurobiol.* **10**, 358 (2000).
37. D. E. Feldman, R. A. Nicoll, R. C. Malenka, *J. Neurobiol.* **41**, 92 (1999).
38. K. Fox, B. L. Schlaggar, S. Glazewski, D. D. O'Leary, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 5584 (1996).
39. V. Rema, M. Armstrong-James, F. F. Ebner, *J. Neurosci.* **18**, 10196 (1998).
40. W. A. Myers, J. D. Churchill, N. Muja, P. E. Garraghty, *J. Comp. Neurol.* **418**, 373 (2000).
41. H. T. Cline, *Curr. Opin. Neurobiol.* **11**, 118 (2001).
42. K. J. Bender, J. Rangel, D. E. Feldman, *J. Neurosci.* **23**, 8759 (2003).
43. K. J. Bender, S. Deshmukh, D. E. Feldman, in *Development and Plasticity in Sensory Thalamus and Cortex,* W. Guido, Ed. (Academic Press, in press).
44. K. J. Bender, C. B. Allen, D. E. Feldman, *Soc. Neurosci. Abstr.* 26.3 (2005).
45. T. Takahashi, K. Svoboda, R. Malinow, *Science* **299**, 1585 (2003).
46. E. Foeller, D. E. Feldman, *Curr. Opin. Neurobiol.* **14**, 89 (2004).
47. T. W. Margrie, M. Brecht, B. Sakmann, *Pfleugers Arch.* **444**, 491 (2002).
48. M. Brecht, M. Schneider, I. Manns, *The Plasticity of the Sensory-Motor Cortices,* F. Ebner, Ed. (CRC Press, in press).
49. Y. Dan, M. M. Poo, *Neuron* **44**, 23 (2004).
50. D. E. Feldman, *Neuron* **27**, 45 (2000).
51. T. Celikel, V. A. Szostak, D. E. Feldman, *Nat. Neurosci.* **7**, 534 (2004).
52. D. E. Shulz, V. Ego-Stengel, E. Ahissar, *J. Physiol.* (Paris) **97**, 431 (2003).
53. G. Feng *et al.*, *Neuron* **28**, 41 (2000).
54. W. Denk, J. H. Strickler, W. W. Webb, *Science* **248**, 73 (1990).
55. B. Lendvai, E. A. Stern, B. Chen, K. Svoboda, *Nature* **404**, 876 (2000).
56. D. B. Chklovskii, B. W. Mel, K. Svoboda, *Nature* **431**, 782 (2004).
57. F. Engert, T. Bonhoeffer, *Nature* **399**, 66 (1999).
58. Q. Zhou, K. J. Homma, M. M. Poo, *Neuron* **44**, 749 (2004).
59. E. S. Ruthazer, H. T. Cline, *J. Neurobiol.* **59**, 134 (2004).
60. M. Maravall, I. Y. Koh, W. B. Lindquist, K. Svoboda, *Cereb. Cortex* **14**, 655 (2004).
61. F. R. Volkmar, W. T. Greenough, *Science* **176**, 1445 (1972).
62. J. T. Trachtenberg *et al.*, *Nature* **420**, 788 (2002).
63. J. Grutzendler, N. Kasthuri, W. B. Gan, *Nature* **420**, 812 (2002).
64. E. J. Green, W. T. Greenough, B. E. Schlumpf, *Brain Res.* **264**, 233 (1983).
65. P. W. Hickmott, P. A. Steen, *Nat. Neurosci.* **8**, 140 (2005).
66. A. K. McAllister, L. C. Katz, D. C. Lo, *Annu. Rev. Neurosci.* **22**, 295 (1999).
67. L. C. Katz, C. J. Shatz, *Science* **274**, 1133 (1996).
68. I. Bureau, G. M. Shepherd, K. Svoboda, *Neuron* **42**, 789 (2004).
69. C. Darian-Smith, C. D. Gilbert, *Nature* **368**, 737 (1994).
70. R. Yuste, T. Bonhoeffer, *Annu. Rev. Neurosci.* **24**, 1071 (2001).
71. A. J. Holtmaat *et al.*, *Neuron* **45**, 279 (2005).
72. Y. Zuo, A. Lin, P. Chang, W. B. Gan, *Neuron* **46**, 181 (2005).
73. M. Matsuzaki, N. Honkura, G. C. Ellis-Davies, H. Kasai, *Nature* **429**, 761 (2004).
74. H. Markram, J. Lubke, M. Frotscher, A. Roth, B. Sakmann, *J. Physiol.* (London) **500** (part 2), 409 (1997).
75. V. Braitenberg, A. Schuz, *Anatomy of the Cortex* (Springer-Verlag, Berlin, 1991).
76. G. W. Davis, C. M. Schuster, C. S. Goodman, *Neuron* **17**, 669 (1996).
77. S. Ramón y Cajal, *Nuevo concepto de la Histología de los Centros nerviosos* (Barcelona, 1893).
78. T. Dittgen *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **101**, 18206 (2004).
79. K. Haas, W. C. Sin, A. Javaherian, Z. Li, H. T. Cline, *Neuron* **29**, 583 (2001).
80. T. W. Margrie *et al.*, *Neuron* **39**, 911 (2003).
81. D. J. Simons, *The Barrel Cortex of Rodents*, E. G. Jones, I. T. Diamond, Eds. (Plenum, New York, 1995), pp. 262–298.
82. Y. Zuo, G. Yang, E. Kwon, W.-B. Gan, *Nature* **436**, 261 (2005).

83. We thank C. Hansel and A. Lee for manuscript comments. This work was supported by NIH R01 NS046652 and the McKnight Foundation (D.F.) and the Erasmus University Rotterdam, a Vidi grant from Netherlands Organization for Scientific Research, and Human Frontier Science Program grants (M.B.).

10.1126/science.1115807

VIEWPOINT

Language Acquisition and Brain Development

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Language acquisition is one of the most fundamental human traits, and it is obviously the brain that undergoes the developmental changes. During the years of language acquisition, the brain not only stores linguistic information but also adapts to the grammatical regularities of language. Recent advances in functional neuroimaging have substantially contributed to systems-level analyses of brain development. In this Viewpoint, I review the current understanding of how the "final state" of language acquisition is represented in the mature brain and summarize new findings on cortical plasticity for second language acquisition, focusing particularly on the function of the grammar center.

A child acquires any natural languages within a few years, without the aid of analytical thinking and without explicit "grammar" instruction as usually taught in school. The origin of grammatical rules should thus be ascribed to an innate system in the human brain (*1*). The knowledge of and competence for human language is acquired through various means and modality types. Linguists regard speaking, signing, and language comprehension as primary faculties of language, i.e., innate or inherent and biologically determined, whereas they regard reading and writing as secondary abilities. Indeed, the native or first language (L1) is acquired during the first years of life through such primary faculties while children are rapidly expanding their linguistic knowledge (*2*). In contrast, reading and writing are learned with much conscious