LTP and LTD as Cellular Mechanisms for Sensory Map Plasticity

The ability of neural circuits to adapt to new experiences and to store information about the environment is central to brain development and learning. An important paradigm for studying this adaptive ability is sensory map plasticity, in which sensory and motor maps are modified based on recent experience, including training on learning tasks. Map plasticity occurs with highly similar functional properties across many brain areas, including primary visual, auditory, somatosensory, and motor cortex (Wiesel and Hubel, 1963; Buonomano and Merzenich, 1998; Sanes and Donoghue, 2000). However, the cellular and synaptic mechanisms that mediate map plasticity are only beginning to be understood.

Long-term potentiation (LTP) and depression (LTD) of cortical synapses emerged as prominent candidate mechanisms for cortical map plasticity relatively soon after the discovery of ocular dominance plasticity in the visual cortex (Stent, 1973; Bear et al., 1987). These mechanisms instantiate Hebbian synaptic plasticity, which can explain many features of cortical map plasticity (Hebb, 1949; Bear et al., 1987; Buonomano and Merzenich, 1998). LTP and LTD are generally hypothesized to mediate rapid components of map plasticity, while anatomical changes that often occur during map plasticity may mediate slower components.

LTD has been hypothesized to play two major roles in map development and plasticity. First, during developmental refinement of topographic projections, LTD is thought to act to weaken aberrant synapses according to Hebbian learning rules, perhaps leading ultimately to synapse elimination (Stent, 1973; Buonomano and Merzenich, 1998). Second, even after maps have formed, patterns of sensory use and disuse powerfully regulate map topography. During this phase, LTD is thought to be involved in weakening excitatory synapses that are underused or behaviorally irrelevant, thus reducing the representation of these inputs in cortical maps (Bear et al., 1987; Singer, 1995; Buonomano...
and LTD may decline somewhat with age, recent studies have clearly demonstrated LTD in adults, indicating that it may contribute to both developmental and adult plasticity (Heynen et al., 1996; Manahan-Vaughan and Braunewell, 1999).

Though LTD has long been hypothesized to contribute to sensory cortical map plasticity, and despite strong evidence for LTD being involved in cerebellar learning (Boyden et al., 2004), direct evidence for LTD in cortical map plasticity was lacking until recently. In this chapter, we review recent evidence that LTD is involved in plasticity of the whisker map in rat primary somatosensory cortex (S1). In S1, both in vivo and in vitro techniques have been used to provide insight into the locus of LTD during plasticity and the induction mechanisms that drive LTD in response to altered experience. This evidence indicates that LTD is a major mechanism for a common feature of cortical map plasticity, the reduction in cortical responsiveness to deprived sensory inputs.

Map Plasticity in Barrel Cortex

In the rat primary somatosensory cortex, the ~30 large facial whiskers are represented by clusters of cells in cortical layer 4 (L4) called barrels. Barrels are arranged in a map isomorphic with the whiskers on the rat’s snout (Woolsey and Van der Loos, 1970; Welker and Woolsey, 1974), and neurons in each barrel are driven best by deflection of a single whisker, termed the principal whisker, which corresponds to the identity of the barrel within the map. Excitatory cells in each L4 barrel make a dense, columnar projection onto layer 2/3 (L2/3) neurons in the cortical column surrounding that barrel, termed the barrel column (Petersen and Sakmann, 2001; Feldmeyer et al., 2002). The vast majority of neurons in each barrel column are driven most strongly by the anatomically appropriate principal whisker, and only weakly by neighboring, surround whiskers (Simons, 1978; Keller, 1995). Thus, an orderly map of whisker receptive fields is present across S1, and the barrels in L4 provide an anatomical reference for this functional whisker map.

The whisker receptive field map in S1 is modifiable by sensory experience. If a whisker is plucked or trimmed for several days or weeks in adolescent animals (7 to ~60 days of age), receptive fields of L2/3 cells within the corresponding column change in two ways. First, L2/3 neurons within the deprived column lose responses to the deprived principal whisker, a phenomenon called principal whisker response depression (PWRD). Second, neurons begin to respond more strongly to neighboring, spared whiskers, termed spared whisker response potentiation (SWRP). These two components of plasticity can be separated genetically and developmentally, indicating that they represent two independent mechanisms for plasticity in S1 (Glazewski and Fox, 1996; Glazewski et al., 2000). Together, PWRD and SWRP cause receptive fields in deprived columns to become dominated by neighboring,
Figure 1  Whisker receptive field plasticity and a possible synaptic basis in rat S1 cortex. A, Receptive field of L2/3 neuron “a”. Principal whisker deprivation causes a rapid (7 days) loss of responses to the deprived, principal whisker, and a slower (20 days) increase in responses to spared, surround whiskers. Dashed lines, control receptive field. Data schematized from Glazewski and Fox, 1996. B, Hypothesized site of LTD mediating principal whisker response depression in adolescent rats.

In animals older than the first postnatal week, PWRD and SWRP occur primarily and most rapidly in L2/3, with less or no receptive field plasticity in L4. This indicates that PWRD and SWRP are mediated by functional changes in intracortical, rather than subcortical, circuits. Substantial progress has been made in identifying the neural basis for PWRD. Fox’s group originally hypothesized that PWRD is due to deprivation-induced weakening, perhaps LTD, of the excitatory L4 to L2/3 projection in deprived columns, which normally drives principal whisker responses in L2/3 (Glazewski and Fox, 1996; Fox, 2002) (Fig. 1B). Strong evidence now exists for this hypothesis (see below). In contrast, the mechanisms underlying SWRP are less clear. SWRP is likely to involve LTP, since transgenic mice with autophosphorylation-incompetent CaMKII, which lack cortical LTP, have substantially impaired SWRP (Glazewski et al., 2000; Hardingham and Fox, 2004). One possibility is that SWRP involves LTP of excitatory trans-columnar projections, which would increase surround whisker responses in L2/3 neurons. However, the site(s) of LTP for SWRP are not yet known, and
other mechanisms besides LTP and LTD are likely to contribute to this and other aspects of whisker map plasticity (e.g., Lendvai et al., 2000; Knott et al., 2002; Shepherd et al., 2003).

Here we summarize recent work focusing on how LTD at the L4-L2/3 excitatory synapse might contribute to the first component of deprivation-induced plasticity, PWRD. This work shows that L4-L2/3 synapses are capable of LTD in vitro, and that whisker deprivation induces marked LTD-like depression of these synapses in vivo. Recordings of spiking patterns in L4 and L2/3 in vivo suggest that this LTD is induced by a reversal in the precise, millisecond-scale timing of L4 and L2/3 spikes during deprivation, which is known to induce spike timing-dependent LTD at this synapse. Finally, anatomical experiments suggest that large-scale changes in L4 neuron number or axonal anatomy do not occur during map plasticity. Therefore, at this synapse, experience primarily regulates synaptic efficacy, not large-scale axonal structure.

**Deprivation Induces LTD-Like Weakening of L4-L2/3 Synapses In Vivo**

To determine if deprivation weakens L4-L2/3 synapses, Allen et al. took advantage of the fact that synaptic and cellular plasticity induced by experience in vivo persists and can be measured in acute, ex vivo brain slices (McKernan and Shinnick-Gallagher, 1997; Finnerty et al., 1999; Rioult-Pedotti et al., 2000). Rats were raised with one or more rows of whiskers plucked starting at postnatal day (P) 12, and slices were prepared 10–20 days later, after whisker map plasticity had presumably occurred (Fig. 2A). Slices were cut in an “across-row” plane that contained one barrel column from each of the 5 rows (termed A–E), so that spared and deprived columns could be identified unambiguously in the slice (Fig. 2B). Bulk synaptic strength of the L4-L2/3 projection was assayed using input-output curves in field potential and whole cell recordings, and was found to be 30–40% weaker in deprived columns than either neighboring, spared columns (Fig. 2C, D) or control columns from sham-plucked littermates (not shown). Plucking did not affect measures of intrinsic postsynaptic excitability, suggesting that the measured depression was due to synaptic changes (Allen et al., 2003).

In more recent experiments, deprivation was shown to increase paired pulse ratios, suggesting that deprivation may decrease release probability at L4-L2/3 synapses (Allen, 2004; K.J. Bender, C.B. Allen, and D.E. Feldman, unpublished data).

To determine whether this deprivation-induced synaptic depression represents a reduction in the strength of preexisting, strong synapses, versus a failure of initially weak synapses to strengthen with development, deprivation was begun at the older age of P20, when synapses are more developed. Four to six days of deprivation starting at P20 caused the same magnitude of synaptic depression as did deprivation from P12,
Figure 2  Whisker deprivation causes LTD-like weakening of L4 to L2/3 excitatory synapses. A, Deprivation of D row whiskers on the snout (X's). B, Living S1 slice containing five barrels corresponding to whisker rows A–E, visualized by transillumination. Stimulation and whole-cell recording sites for studying L4-L2/3 synapses are shown. C, Family of EPSPs in response to increasing stimulation intensity in L4, for two cells in a deprived D column, and 2 cells in the spared B column of the same slice. D, Comparison of mean EPSF amplitude between deprived and spared columns. All amplitudes are normalized to the mean maximal amplitude in the non-deprived column of each slice. E, Occlusion of LTD by whisker deprivation. LFS, 900 presynaptic stimuli at 1 Hz. Bars are S.E.M. Data from Allen et al., 2003.

suggesting that deprivation does not simply cause a failure of synaptic development, but actively weakens existing synapses. In addition, the time course of depression was determined by recording in slices made from animals deprived of whiskers for 3, 5, and 7 days, beginning at P12. Significant synaptic depression was observed after 5 days of deprivation, but not 3 days, suggesting that 4–5 days of deprivation are required to alter synaptic strength at these ages (Allen, 2004).

To determine whether deprivation-induced synaptic weakening represents LTD, Allen et al. tested for occlusion. Because LTD is typically a saturable phenomenon (Dudek and Bear, 1992; Mulkey and Malenka, 1992; Lebel et al., 2001), LTD induced by deprivation in vivo should occlude further LTD induction in vitro. Results showed that deprivation-induced synaptic weakening profoundly occluded LTD induction by low frequency stimulation (900 pulses at 1 Hz) (Fig. 2D). Consistent with the occlusion model, the capacity for LTP was enhanced by deprivation, indicating that deprived synapses were not merely deficient in plasticity. These findings were recently replicated (Hardingham and Fox, 2004). Thus, these experiments demonstrate that whisker deprivation reduces the physiological strength of L4-L2/3 synapses via LTD or an LTD-like mechanism. Similar results have been found for monocular deprivation, which causes both physiological and biochemical signatures of LTD at
L4-L2/3 synapses in visual cortex (Heynen et al., 2003). Together, these results suggest that LTD is likely to be an important mechanism for plasticity in S1 and V1. Whether deprivation also weakens circuits through reduction in synapse or neuron number is addressed by experiments below.

How is LTD Induced During Sensory Deprivation In Vivo?

At L4-L2/3 synapses in vitro, like at many excitatory synapses, LTP and LTD can be induced by multiple induction protocols. These include altering presynaptic firing rate (termed rate-dependent plasticity) (Madison et al., 1991; Linden and Connor, 1995), and modulating the relative timing of pre- and postsynaptic spikes on a millisecond timescale, largely independent of firing rate (spike-timing dependent plasticity, STDP) (Dan and Poo, 2004). Most models of experience-dependent cortical plasticity assume rate-dependent induction of LTP and LTD. However, Celikel et al. conducted experiments to determine which of these modes of LTP/LTD induction drives LTD at L4-L2/3 synapses in S1 in response to whisker deprivation and found strong evidence that STDP is the relevant mechanism (Celikel et al., 2004).

L4-L2/3 synapses in visual cortex exhibit a standard rate-dependent LTP/LTD learning rule in which presynaptic firing rates of a few Hz drive LTD, and rates >10 Hz drive LTP (Fig. 3A). Though the full learning rule is not known in S1, its basic form is similar, with a cross-over point between LTP and LTD at about 10 Hz (S. Bergquist and D.E. Feldman, unpublished data). To determine whether deprivation alters spike rate in a manner appropriate to drive rate-dependent LTD at L4-L2/3 synapses in vivo, Celikel et al. made extracellular recordings from L4 and L2/3 neurons in awake, behaving rats. When all whiskers were intact, L4 and L2/3 neurons fired at mean rates of 2.7 and 2.1 Hz, respectively, across several whisker-related behavioral states. Trimming of the...
principal whisker corresponding to the recorded column caused mean firing rates to reduce, but only modestly, to 2.1 and 1.7 Hz, respectively (Fig. 3B). Because 2–4 Hz firing elicits similar, near-maximal LTD at L4-L2/3 synapses in V1, as well as in CA1 hippocampus, it seems unlikely that these modest changes in spike rate could drive rate-dependent LTD in vivo (Dudek and Bear, 1992; Bear, 1996; Kirkwood et al., 1996; Huber et al., 1998) (Fig. 3A). Indeed, the low frequency of firing observed with all whiskers intact suggests that precise spike timing, rather than firing rate, may be most relevant for plasticity in vivo.

How spike timing may drive LTD in vivo can be inferred from the precise shape of the STDP learning rule measured in vitro. LTP is induced at L4-L2/3 synapses when presynaptic spikes lead postsynaptic spikes by 0–15 ms. In contrast, LTD results when postsynaptic spikes lead presynaptic spikes by a longer interval of 0–50 ms (Fig. 3C). The longer temporal window for LTD predicts that LTD can be induced in vivo by two means: either by reliable post-leading-pre firing within the LTD window, or by uncorrelated spiking at low rates, which drives net LTD because uncorrelated spike trains contain more interspike delays that fall within the long LTD window than delays that fall within the brief LTP window (Feldman, 2000).

To determine whether deprivation may drive spike timing-dependent LTD in vivo, Celikel et al. measured the spiking of L4 and L2/3 neurons simultaneously in the same barrel column in anesthetized rats. To mimic normal whisking, all whiskers were deflected together by inserting them into a piezoelectric-driven plastic mesh. Under this condition, L4 neurons faithfully spiked several milliseconds before neurons in L2/3, a pre-leading-post firing order that is appropriate to drive spike timing-dependent LTP (Fig. 4). To simulate whisker deprivation, the principal whisker was cut to narrowly escape the mesh, so that the mesh now deflected all whiskers but the principal whisker. This resulted in two immediate changes in L4 and L2/3 firing correlations in the deprived column. First, mean firing order reversed, with most L2/3 neurons now spiking before L4 neurons (Fig. 4). This reversal was most pronounced between L4 and L2 neurons. Second, overall firing correlations between pairs of L4 and L2/3 neurons significantly decreased (not shown). These changes recovered immediately when the principal whisker was reinserted into the mesh. Thus, whisker deprivation acutely altered spike timing at L4-L2/3 synapses in a manner that was exactly appropriate to drive spike timing-dependent LTD (Celikel et al., 2004).

These experiments suggest that spike timing, not spike rate, is the key feature of S1 spike trains that drives deprivation-induced weakening of L4-L2/3 synapses, and that STDP is the relevant mode of LTD induction. However, it will be critical to verify that these use-dependent changes in spike timing occur in awake-behaving, not just anesthetized, rats. In addition, the prevalence of STDP as a learning mechanism in vivo needs to be examined. Is it most relevant only in sparsely spiking brain regions, like S1, in which rate-dependent plasticity is unlikely, or is it utilized more generally?
Figure 4  Acute deprivation of a single principal whisker causes a reversal in L4-L2/3 firing order appropriate to drive spike timing-dependent LTD in vivo. A, Spike trains of a pair of L4 and L2 neurons, recorded simultaneously in a single S1 column, under 3 sequential conditions: simultaneous deflection of all whiskers, deflection of all but the principal whisker (PW cut, to mimic acute deprivation of one whisker), and all-whisker deflection (recovery). Note reversal in L4-L2 firing order during PW cut. B, Peristimulus time histograms of L4 and L2 responses for each stimulus condition (900 stimulus repetitions). Stimulus onset, 0 ms. C, Cross-correlograms representing relative timing of L4 and L2 spikes during sensory responses in each condition. Data from Celikel et al., 2004.

Deprivation does not Alter the Anatomy of L4-L2/3 Projection

In mature S1, excitatory cells within L4 barrels extend dense, ascending axonal projections to L2/3. These projections are highly column-specific, preferentially targeting L2/3 within the home column (Petersen and Sakmann, 2001; Feldmeyer et al., 2002). This columnar precision is thought to be important for conferring appropriate principal whisker responses in L2/3 neurons. As for many projections, there is a debate over whether the L4-L2/3 axonal projection arises during development from an initially precise or imprecise projection. Axonal reconstructions from biocytin-filled L4 neurons in thick S1 slices (400 µm) showed that roughly one third of L4 spiny neurons extended non-column specific axonal arbors at P8-10, and that column specificity developed by P14 through selective addition of branches in the correct target column (Bender et al., 2003). However, another study that used axonal fills and
functional mapping of projections in thinner slices (300 µm) found that initial axons showed adult-like columnar precision (Bureau et al., 2004). Whether this discrepancy arises from loss of longer, non-columnar axonal branches in thin slices is unclear. However, both studies do make clear that axons are still growing during the developmental period in which whisker deprivation induces weakening at L4-L2/3 synapses. Therefore, deprivation-induced changes in arbor size, arbor topography, and synapse number need to be considered as additional possible mechanisms for deprivation-induced weakening of the L4-L2/3 synaptic connection.

To test whether deprivation alters L4 axonal morphology or synapse number, axonal arbors of L4 excitatory cells projecting to L2/3 were examined using single-cell reconstructions (Bender et al., 2003). Animals were raised with all whiskers intact or the D-row deprived from P8 to P23-26, a manipulation known to drive synaptic depression at this projection (Allen et al., 2003). Slices were cut in the across-row plane to contain one barrel from each row. Excitatory spiny stellate and star pyramidal cells in the center of the D-barrel were filled with biocytin during whole-cell recording and visualized with a diaminobenzidine-based reaction (Fig. 5A). Axonal reconstructions were made relative to column boundaries, determined by counterstaining for L4 barrels with osmium tetroxide (Fig. 5B).

To determine whether deprivation reduced axonal length or distribution in L2/3, we quantified the length of axon in L2/3 as a function of location tangential to the pial surface. In control rats, the projection was largely columnar, with ~90% of axon in L2/3 contained in the home (D) column. D-row deprivation did not alter the tangential distribution of this projection, or the total length of each axon in L2/3 (Fig. 5C, D). Deprivation of all contralateral whiskers (A–E rows) also produced no detectable effect on axonal length or topography (Bender et al., 2003; Bureau et al., 2004).

As a first step in determining whether deprivation reduced synapse number, we calculated axonal bouton density for randomly selected axon segments in L2/3. Bouton density is relatively constant across axonal branches for cortical excitatory cells (Yabuta and Callaway, 1998; Bender et al., 2003). Deprivation did not detectably alter bouton density, suggesting that anatomical synapse number remains constant during sensory deprivation, despite the 40% reduction in bulk synaptic strength shown above (Fig. 5E). It is important to stress that these results show only that deprivation does not lead to massive synaptic withdrawal observable at the light level, and that ultrastructural changes including changes in the number of release sites per bouton may still occur.

Whisker deprivation may also reduce L4-L2/3 connection strength by reducing the number of L4 neurons in deprived barrels, rather than decreasing the number of L4-L2/3 synapses per L4 axon. Since barrel size does not change with deprivation (Fox, 1992), we estimated changes in cell number by calculating cell density within L4 barrels in control and whisker deprived animals. In these experiments, which have not
Figure 5 Whisker deprivation does not alter gross anatomy of L4 axons in L2/3. A, Single-section montage showing biocytin-labelled L4 spiny stellate neuron. Inset, High power view showing axonal boutons (arrows). B, Full reconstruction of neuron in (A). Barrel position was determined from neighboring osmium tetroxide-stained section. Black: dendrite. Grey: axon. Light grey: barrel outlines and pia. Numbers indicate layers. C, Distribution of axon tangential to the pial surface for control and D-row deprived rats. Bars are SEM. Ellipses show approximate barrel boundaries. D and E, Deprivation of D row whiskers did not alter total axon length or bouton density in layers 1–3. Bars are mean. Triangles, age-matched control and deprived rats. Data from Bender et al., 2003.

been previously reported, Long-Evans rats were D-row deprived from P12-P23, or had normal whisker experience. Rats were perfused at P23 with 4% paraformaldehyde, the contralateral hemisphere was sectioned at 40 µm in the across-row plane, and alternate sections were stained for NeuN, a neuron-specific nuclear protein, or cytochrome oxidase (CO) to visualize barrels. NeuN staining (mouse anti-NeuN, Chemicon, 1:1000 dilution, 18 hr at 4ºC) was visualized using a fluorescent secondary antibody (Alexa-488 anti-mouse, Jackson ImmunoResearch, 1:1000, 1 hr at 25ºC). NeuN-immunoreactive neurons were marked using Neurolucida software (Microbrightfield) with the experimenter blind to deprivation history and barrel boundaries. Barrel boundaries were then projected from neighboring CO sections (Fig. 6A, B). Neuronal density was calculated for B–E barrels in 3 separate slices per animal, and corrected for 2% tissue shrinkage, assessed by comparing the average distance between C, D, and E barrel centroids in fixed, CO-stained tissue, versus living, transilluminated acute brain slices. Shrinkage values matched previous measurements in our lab (Bender et al., 2003).
Results showed that neuronal density was constant across B–E barrels for both control rats (n = 3) and D-row deprived rats (n = 2) (Fig. 6C). Across all sections, the average neuronal density within barrels was 122,000 ± 4,000 neurons/mm³ (mean ± S.E.M). At this density, an average barrel, approximated as a cube of across-row width 460 µm, within-row width 410 µm, and height 310 µm, would contain roughly 7000 neurons. Deprivation did not appear to alter neuronal density in the deprived D column (Fig. 6C).

Together, these anatomical results indicate that deprivation-induced map plasticity does not involve large scale loss of L4 neurons or axons.
Instead, deprivation seems to reduce the physiological strength of L4-L2/3 synapses while gross anatomical features of the projection remain intact. Similar results have been observed in the barn owl sound localization system. In the barn owl, auditory-visual misalignment induced by wearing prismatic spectacles causes visually guided learning of sound localization. This learning involves the loss of pre-existing, inappropriate auditory responses, and the growth of new axonal projections to mediate new auditory responses appropriate to the visual displacement. Axonal connections mediating normal auditory responses persist with extended prism experience, even though these responses are physiologically reduced or absent, suggesting that experience weakens functional synaptic efficacy but does not cause gross synaptic withdrawal (DeBello et al., 2001). Similarly, new axonal connections formed during learning remain anatomically intact even after they are functionally silenced by prism removal (Linkenhoker et al., 2005).

Why deprivation appears to affect synaptic efficacy but not axonal anatomy of L4 cells is unclear, especially because in visual cortex, axonal restructuring of thalamocortical and L2/3 horizontal axons does occur during deprivation-induced map plasticity (Antonini and Stryker, 1993; Darian-Smith and Gilbert, 1994). Similarly in S1, all-whisker unilateral deprivation does alter the branch structure of L2/3 pyramidal cells at these ages (Maravall et al., 2004), indicating that cortical neurons are capable of experience-dependent anatomical plasticity. Perhaps L4 axons could undergo anatomical plasticity given longer deprivation durations.

Conclusions

Work presented here suggests that LTD or LTD-like synaptic depression is an important component of developmental map plasticity in sensory cortex. A working hypothesis for how LTD is induced by deprivation is summarized in Fig. 7. In this hypothesis, feedforward connectivity from thalamus to L4 to L2/3 ensures that during normal sensory use, most L4 spikes occur before L2/3 spikes. Deprivation causes immediate reversal in firing order for L4 and L2/3 neurons (illustrated) and decreases overall firing correlations (not shown), with little change in spike rate. What cortical circuits mediate the firing order reversal are not yet clear, although trans-columnar excitatory inputs from surrounding columns with intact whiskers seem well-suited to mediate the residual L2/3 responses in deprived columns. We hypothesize that these acute changes in spike timing, over several days, drive spike timing-dependent LTD at L4-L2/3 synapses, and that this LTD is a primary mechanism for weakening of responses to the deprived principal whisker in L2/3. Anatomical measurements indicate that this reduction in L4-L2/3 synapse efficacy occurs without large-scale changes in L4 cell number, axonal anatomy, or bouton number, although changes in dendrites, spines, and synaptic ultrastructure may occur (Lendvai et al., 2000; Maravall et al., 2004).
Figure 7 Model for deprivation-driven induction of LTD at L4-L2/3 synapses in vivo. Left, When all whiskers are intact, deflection of the principal whisker drives spikes from L4 neurons, which in turn activate L2/3 neurons via ascending, feedforward L4-L2/3 synapses. Thus, L4 neurons tend to spike before L2/3 neurons. Middle, whisker deprivation is known to acutely alter L4-L2/3 firing correlations in two ways: firing order reverses, so that L2/3 neurons tend to fire before L4 neurons (illustrated), and L4 and L2/3 spike trains become decorrelated (not illustrated). Together, these changes in spike timing are hypothesized to drive spike timing-dependent LTD at L4-L2/3 synapses (right panel).

If whisker deprivation causes immediate reversal of L4-L2/3 spike timing, and spike timing-dependent LTD occurs rapidly in vitro (within minutes), why is 5 days of deprivation required for measurable weakening of L4-L2/3 synapses in vivo? One likely factor is that in behaving animals, only a small fraction of total spikes in a given S1 column are driven by whisker deflections, with the rest being spontaneous or driven by whisker self-motion (Fee et al., 1997). Because deprivation only alters the timing of whisker-driven spikes, deprivation may produce only relatively small biases of overall spiking statistics, leading to relatively slow accrual of timing-dependent LTD. Another related factor is that ongoing, spontaneous network activity is known to powerfully reverse recently induced LTP and LTD, which could slow the accrual of these forms of plasticity in vivo (Xu et al., 1998; Zhou et al., 2003). Third, receptive field plasticity is known to be faster when whiskers are plucked singly or in a checkerboard pattern, so that each deprived column has many spared neighboring columns (Fox, 2002). In our studies of deprivation-induced synaptic weakening in vivo, we plucked whole rows of whiskers, thus leaving fewer spared whiskers around each deprived whisker. We are currently investigating whether this pattern of plucking may alter spike timing more modestly than single-whisker deprivation, which could explain the slower development of synaptic plasticity in this case.
Several key experiments are also necessary to test the working hypothesis in Fig. 7. First, it is unknown whether the changes in spike timing observed with acute whisker deprivation in anesthetized animals occur similarly in awake-behaving animals. Second, current evidence is only correlative that LTD contributes to receptive field plasticity; tests for causality are required. To test causality, it will be necessary to selectively block or manipulate LTD, either pharmacologically or genetically, and to determine if whisker map plasticity is altered or impaired. In visual cortex, this strategy has produced mixed results, so the causality of LTD in ocular dominance plasticity remains unknown (Hensch and Stryker, 1996; Renger et al., 2002; Fischer et al., 2004). To resolve this issue it will be critical to improve our understanding of the molecular basis of LTD at relevant cortical synapses, in order to develop more selective and effective reagents that interfere with LTD. These reagents could then be used to probe the role of LTD in cortical map plasticity.

References


