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Rate and timing in cortical synaptic plasticity

Sacha B. Nelson*, Per Jesper Sjöström and Gina G. Turrigiano

Department of Biology and Volen Center for Complex Systems, Brandeis University, Mailstop 008, 415 South Street, Waltham, MA 02454-9110, USA

Debate has raged over the past few years as to whether cortical neurons transmit information primarily in their average firing rates or in the precise timing of their spikes. Here, we address the related question of which features of spike trains control plasticity at cortical synapses. Using paired recording in slices we have developed a quantitative and predictive description of the joint dependence of cortical plasticity on the rate and relative timing of pre- and postsynaptic firing. The results hold important implications for which parts of the neural code are most readily stored for later retrieval.

Keywords: long-term potentiation; long-term depression; spike timing

1. INTRODUCTION

Altering sensory experience, both during development and in the adult, can lead to potent changes in the organization of cortical receptive fields. A common theme of these plasticity experiments is that neurons representing parts of the periphery which are stimulated together become strengthened and linked, while neurons representing parts of the periphery which are lesioned or stimulated in an uncorrelated fashion become weakened and disconnected. Depending on the paradigm, many mechanisms, both within the cortex and more peripherally, may contribute, but it is widely assumed that Hebbian plasticity at cortical synapses is a key component of experience-dependent changes in sensory representation (Katz & Shatz 1996). Despite the attractiveness of this idea, it has been difficult to formulate it in a rigorous and quantitative way. A quantitative formulation requires that we know not merely that 'neurons that fire together wire together', but precisely how much firing at what frequency and with what degree of correlation are required.

At hippocampal and neocortical synapses, the sign and magnitude of plasticity are strongly rate dependent. LTP is induced when afferents are stimulated at high rates, while lower rates of activity produce LTD (Dudek & Bear 1992; Kirkwood *et al.* 1993). But in addition to depending on the rate, the induction of plasticity also depends on the precise timing of pre- and postsynaptic firing (Bi & Poo 1998; Debanne *et al.* 1998; Egger *et al.* 1999; Feldman 2000; Markram *et al.* 1997; Zhang *et al.* 1998; see also earlier studies by Levy & Steward 1983; Gustafsson *et al.* 1987; Debanne *et al.* 1994). We refer to this phenomenon as STDP (Abbott & Nelson 2000). At excitatory synapses onto cortical and hippocampal pyramidal neurons, pre-before-post spiking within a 10 ms timing window gives rise to LTP, whereas post-before-pre firing produces LTD. Mechanistically, this timing requirement is thought to depend upon nonlinear summation of voltage (Stuart & Häusser 2001) and calcium signals (Yuste & Denk 1995; Magee & Johnston 1997; Koester & Sakmann 1998; Schiller *et al.* 1998, 2000) produced by EPSPs and back-propagating APs.

Rate-dependent and timing-dependent induction of cortical plasticity have served as starting points for influential models of cortical learning and development. Rate-based models typically ignore the details of timing (Von der Malsburg 1973; Bienenstock *et al.* 1982), while spike-timing based models have typically disregarded the dependence of learning rules on rate (Gerstner *et al.* 1996, Song *et al.* 2000, Van Rossum *et al.* 2000). The integration of these two parameters into a single learning rule is not trivial. For example, at high rates (e.g. 50 Hz) a single post-synaptic AP can occur at a time that is both immediately before one presynaptic AP, and immediately following another. Predicting the build-up of plasticity during natural patterns of firing requires knowing how plasticity signals from these multiple timing relationships are integrated (figure 1).

In addition to depending upon the precise temporal structure of coincident firing, the induction of plasticity can also depend on the number of coincident inputs. In early studies, this dependence was termed cooperativity: tetanization of a weak pathway produced potentiation only if in synchrony with a stronger pathway (McNaughton *et al.* 1978; Levy & Steward 1979; Barrionuevo & Brown 1983; Kirkwood & Bear 1994; Debanne *et al.* 1996). More recently, cooperativity has been presumed to reflect the fact that unitary inputs produce small depolarizations that are insufficient to allow enough NMDA-mediated calcium influx to produce LTP (Bliss & Collingridge 1993). A prediction of this view is that STDP should not exhibit cooperativity, since in these protocols the postsynaptic APs are provided, which should unblock NMDA receptors. Our experiments revealed a novel form of cooperativity present even when appropriately timed postsynaptic APs are provided.

*Author for correspondence (nelson@brandeis.edu).

One contribution of 22 to a Discussion Meeting Issue 'The essential role of the thalamus in cortical functioning'.

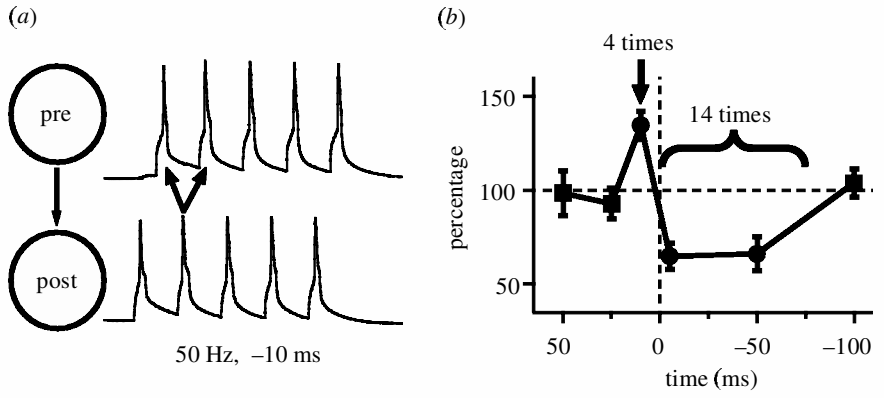

Figure 1. Multiple timing relationships during high-frequency firing. (*a*) Postsynaptic cell fires 10 ms after presynaptic cell at 50 Hz. (*b*) Spike-timing curve at low frequency (0.1 Hz) shows LTP (more than 100%) for pre-before-post firing (positive values of time axis), and LTD (less than 100%) for post-before-pre firing (negative values of time axis). Note that the firing pattern on the left contains both pre-before-post and post-before-pre relationships (e.g. arrows). Counting all possible interactions that fall between +15 and –75 ms, there are four pre-before-post and 14 post-before-pre.

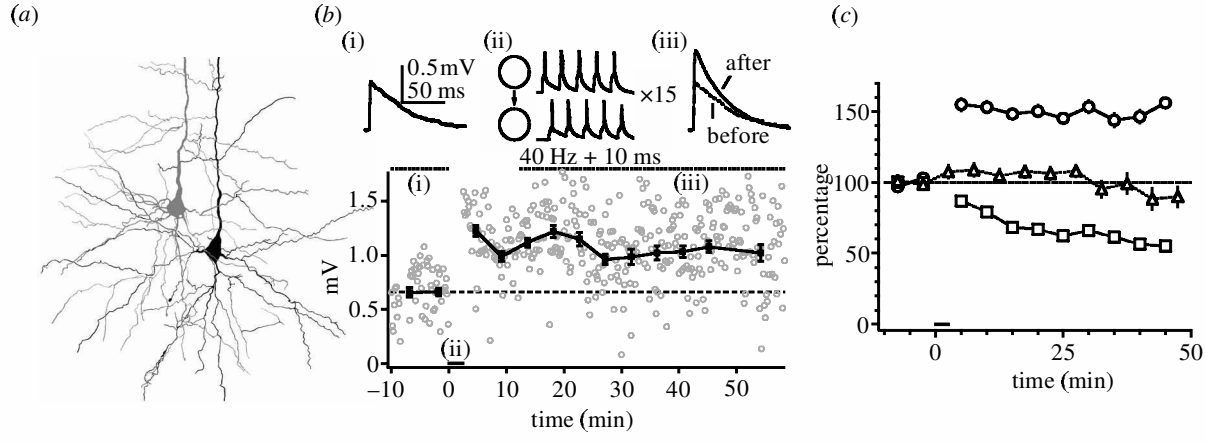

Figure 2. Spike-timing dependent plasticity at synapses between thick tufted layer-5 cortical pyramidal neurons. (*a*) *Camera lucida* drawing of pre- (left) and postsynaptic neurons; responses shown in (*b*). (*b*) LTP induction at 40 Hz. Top, individual response amplitudes (open circles) and 5 min averages (black circles). Pre- and postsynaptic input resistance, membrane potential (lower traces) remained stable. The right-hand traces illustrate average unitary EPSPs before and after (i,iii) induction (ii), consisting of 15 bursts of five spikes at 40 Hz with presynaptic spikes preceding postsynaptic spikes by 10 ms (+10 ms). Average EPSP amplitude was potentiated by 163% (after–before, $p < 0.01$). (*c*) Pre-before-post firing (+10 ms) at frequencies between 10 and 50 Hz produced LTP (circles, $n = 21$), while post-before-pre firing (–10 ms) at frequencies between 0.1 and 20 Hz produced LTD (squares, $n = 14$). Low-frequency pairing at large temporal offsets (+400 ms) produced little change in EPSP amplitude (triangles, $n = 8$). (Adapted from Sjöström *et al.* (2001).)

2. INDUCTION OF LTP AT LAYER-5 SYNAPSES DEPENDS JOINTLY ON RATE, TIMING AND COOPERATIVITY

We made whole-cell recordings from synaptically connected thick tufted layer-5 neurons in slices of rat visual cortex (figure 2*a*). The quantitative description of the rate and frequency dependence of LTP and LTD induction at these synapses was based on recordings from 239 connected pairs (of 1604 tested).

As previously reported for paired recordings in somatosensory cortex (Markram *et al.* 1997), LTP was induced when presynaptic spikes preceded postsynaptic firing by 10 ms, and LTD resulted when the timing was reversed. However, unlike several prior reports employing extracellular stimulation (Feldman 2000) or paired recording in culture (Bi & Poo 1998; Debanne *et al.* 1998), LTP was not present at low frequency (0.1 Hz). Potentiation at low frequency could, however, be rescued by providing additional depolarization immediately preceding the postsynaptic AP, either via simultaneously stimulating other inputs extracellularly, or by direct subthreshold somatic current injection (see Sjöström *et al.* 2001, figs 2–4). The same subthreshold current injection without the postsynaptic spike, however, led to LTD (Artola *et al.* 1990), consistent with the view that LTP 'wins out' over LTD (see § 5).

When using extracellular stimulation, EPSPs greater than 2–3 mV potentiated, while smaller EPSPs did not. Presumably this threshold, measured at the soma, reflects a requirement for substantially greater dendritic depolarization. The amplitude of this depolarization requirement is comparable with that previously reported to rescue backpropagation of APs within the distal apical dendrite (Stuart & Häusser 2001).

Given the requirement for depolarization of the postsynaptic neuron of *ca.* 2–3 mV immediately prior to the

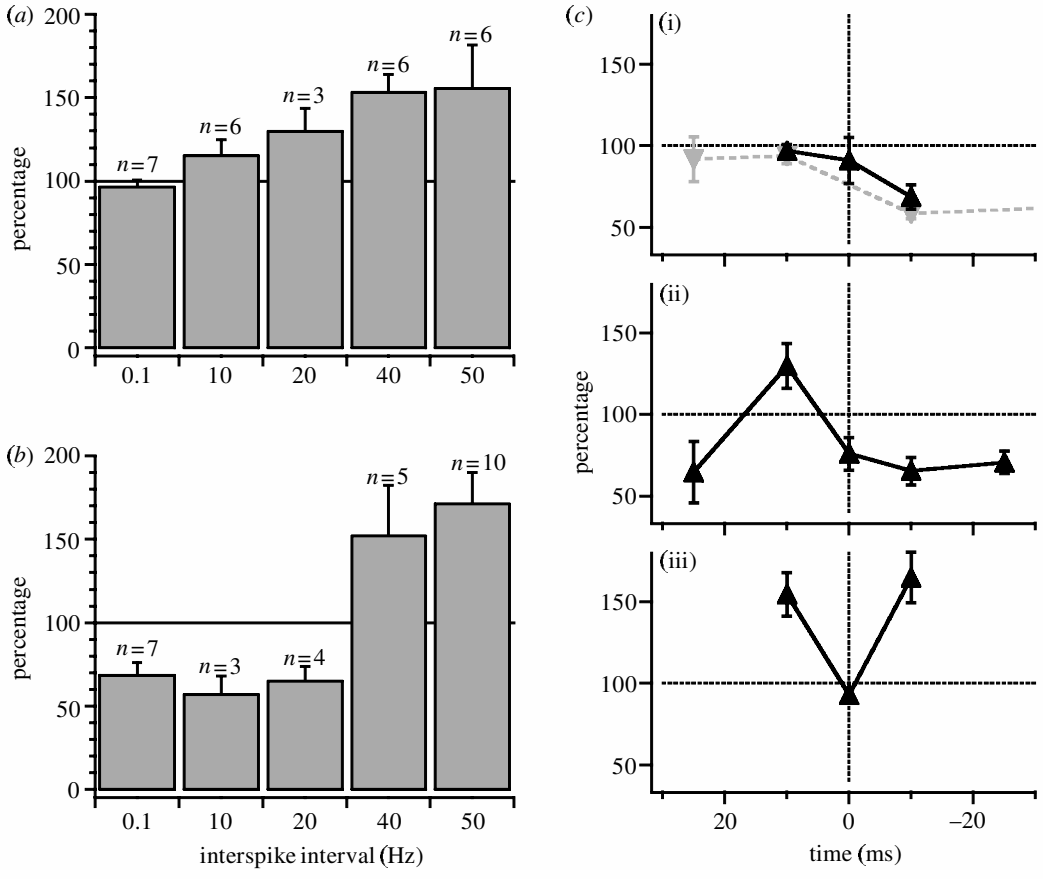

Figure 3. LTP, LTD and spike-timing curves vary with frequency. (*a*) Pre-before-post firing (10 ms) evokes increasing LTP with increasing frequency. (*b*) By contrast, post-before-pre firing (−10 ms) evokes a constant amount of LTD between 0.1 and 20 Hz, but evokes LTP at 40 and 50 Hz. (*c*) Spike-timing curves obtained at (i) 0.1, (ii) 20 and (iii) 40–50 Hz differ dramatically. Depression predominates at low frequency, whereas potentiation is more prevalent at high frequencies. Positive offsets are pre-before-post, negative are post-before-pre. Results from paired recordings. Note, however, that plasticity is strongly timing dependent at all frequencies. The *n* values are between 3 and 7 per point, except for +10 ms and –10 ms at 40–50 Hz ($n = 12$ and 15, respectively). Dashed line at 0.1 Hz shows extracellular stimulation experiments for EPSPs < 2.3 mV for comparison. (Adapted from Sjöström *et al.* (2001).)

postsynaptic AP, and an average unitary EPSP of 0.73 mV, cooperative firing of several neurons is required to induce LTP at low frequency. A Monte Carlo simulation based on the distribution of amplitudes of 139 connections indicated that, on average, 5.4 ± 1.5 s.d. layer-5 neurons would have to cooperate to produce LTP. Prior studies have concluded that cooperativity reflects the cooperation needed to evoke a postsynaptic AP and unblock NMDA receptors. The cooperativity demonstrated in these experiments differs from that identified previously because it is present even though we are supplying an appropriately timed postsynaptic spike.

The requirement for depolarization preceding the postsynaptic spike also contributed to the observed frequency dependence of LTP induction. During high-frequency bursts the postsynaptic membrane potential did not entirely repolarize between APs. Removing this residual depolarization by hyperpolarizing the membrane back to rest between APs blocked LTP induction at high frequency. The depolarization, although necessary for LTP induction, was insufficient to explain its frequency dependence, since maximal depolarization at low frequency produced significantly less LTP than was observed at high frequency. On the basis of these and other observations, we conclude that there are two components to the observed frequency dependence:

(i) a voltage threshold for LTP induction that residual depolarization during high-frequency firing can overcome (see Sjöström *et al.* 2001, figs 4 and 5*a*); and
(ii) a more graded dependence on pairing frequency, perhaps reflecting a leaky integrator of the signalling events (e.g. calcium or a downstream signal) giving rise to LTP.

3. INDUCTION OF LTD IS INDEPENDENT OF DEPOLARIZATION AND IS ABSENT AT HIGH FIRING RATES

Unlike LTP, the induction of LTD did not require a threshold depolarization preceding the postsynaptic spike, and exhibited a very different frequency dependence. LTD was constant over the range of 0.1–20 Hz, but was absent at higher frequencies (figure 2). At these frequencies (e.g. 40 and 50 Hz) multiple spike timings occur (see figure 1). Each presynaptic spike occurring 10 ms after the preceding postsynaptic spike is also 10 or 15 ms

before the subsequent postsynaptic spike, a timing relationship that gives rise to LTP. We found that in these cases no LTD was induced. For example, in bidirectionally connected pairs ($n = 7$), the same firing is pre-before-post in one direction and post-before-pre in the other direction, yet comparable amounts of LTP were induced in both directions.

Due to the differences in the frequency dependence of LTP and LTD (figure 3*a*,*b*), the shape of the spike-timing curve changed with frequency (figure 3*c*). However, even at high frequencies, plasticity was strongly timing dependent; pre-before-post spiking at 40 or 50 Hz produced strong LTP, while pre- and postsynaptic spiking with zero time delay left the synaptic strength unchanged. Synchronous firing did evoke LTP at 100 Hz (not shown), but at this frequency each presynaptic spike (except the last in a burst) precedes the subsequent postsynaptic spike by 10 ms.

4. AN EMPIRICAL MODEL OF STDP INDUCTION

Prior theoretical studies have often assumed that the build-up of STDP can be adequately modelled by linear summation of plasticity increments derived from the low-frequency timing curve. However, our results indicate that this is not likely to work, since both LTP and LTD induction depend on the rate. In addition, as mentioned in § 1, it is unclear which spike-timing relationships should be counted. Most models have counted all pairs of pre- and postsynaptic spikes (Song *et al.* 2000), while some models have counted only neighbouring spikes (Van Rossum *et al.* 2000).

We found that the behaviour at all frequencies could be understood in terms of a single underlying spike-timing curve and a few simple rules. These are as follows.

(i) There is a roughly sigmoidal relationship between the postsynaptic voltage immediately preceding the spike and LTP at low frequency.
(ii) There is an additional frequency-dependent component of LTP that is linear in frequency.
(iii) For multiple timing interactions, only the nearest-neighbour interactions are counted (in other words if a postsynaptic spike is followed by two presynaptic spikes the LTD produced is the same as if it was followed by a single presynaptic spike).
(iv) When a postsynaptic spike both follows (LTP promoting) and precedes (LTD promoting) a presynaptic spike, only the LTP-promoting timings are counted.

These rules were implemented in a simple model designed to predict the build-up of plasticity during any pattern of pre- and postsynaptic firing (figure 5). The only free parameters of the model were the slope and intercept of the additional linear frequency dependence of LTP (step 3 in figure 5). Three variants of the model (figure 4) were then fitted to the LTP (pre-before-post) or LTD (post-before-pre) induction experiments across frequencies. In order to test the predictive value of the model, we then performed additional experiments in which the timing of pre- and postsynaptic spikes was jittered so that all relative spike timings between +20 and −20 ms were represented so as to approximate random firing. As shown previously for extracellularly evoked EPSPs in layer 2/3 (Feldman 2000), low-frequency firing in which relative timing was randomized produced LTD. But, as the frequency increased, the same random timings produced increasing LTP. This behaviour was accurately predicted by the model (figure 6). The prediction was most accurate when only local interactions between pre- and postsynaptic APs were included, and when LTD-promoting interactions were overruled by LTP-promoting interactions involving the same presynaptic spike. The variant of the model in which all interactions were counted performed especially poorly since it tended to over-predict the amount of LTD observed at high frequency.

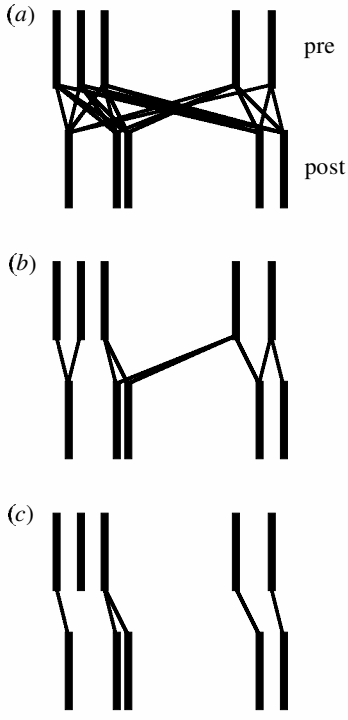

Figure 4. Three variant models for integration during STDP induction. The models differ in which pre- and postsynaptic spike pairs are integrated in calculating the total build-up of plasticity. In each case, pre- and postsynaptic spikes are represented as thick vertical lines and interactions leading to plasticity are indicated with diagonal lines. In model 1 (*a*) all pre- and postsynaptic spikes are allowed to interact. In models 2 (*b*) and 3 (*c*) only neighbouring spikes are allowed to interact. Finally, in model 3, LTP-promoting interactions (pre-before-post) are presumed to win out over LTD-promoting interactions (post-before-pre) when they involve the same postsynaptic spike.

5. DISCUSSION

The simulations and experiments reviewed here indicate that the build-up of plasticity at thick tufted layer-5 pyramidal neurons can be predicted from the combined voltage, timing and rate dependence of LTP and LTD induction. Our results are consistent with the view that rate- and timing-based models represent partial and complementary descriptions of a single set of underlying plasticity mechanisms.

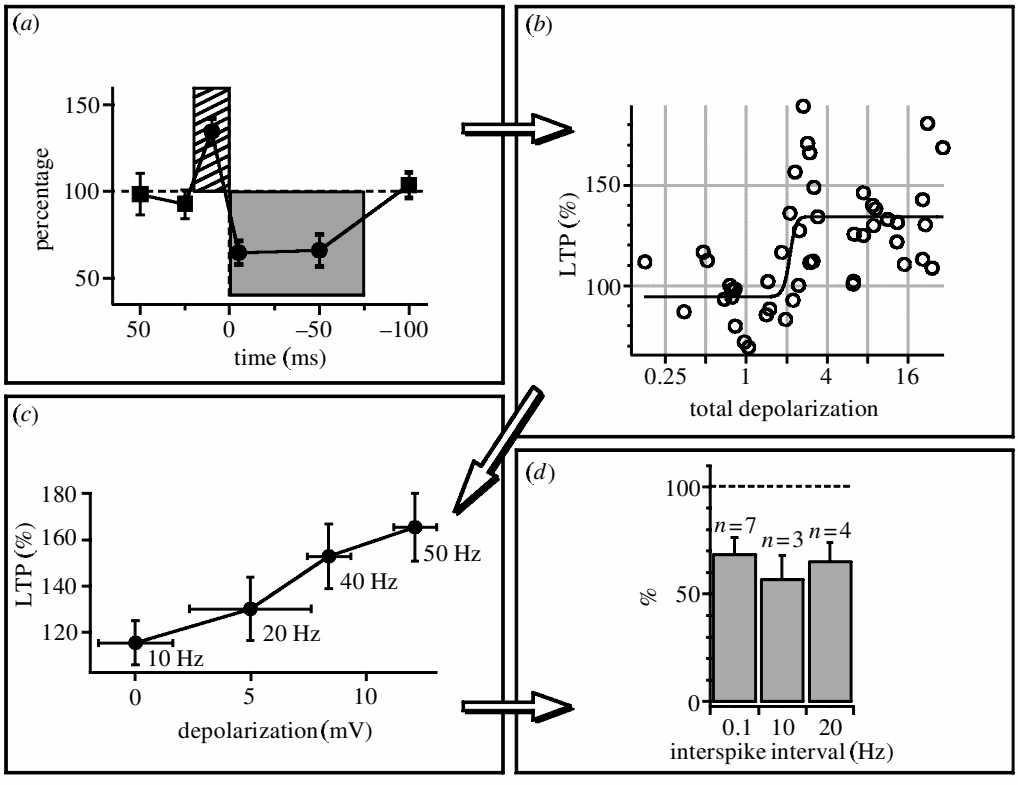

Figure 5. Procedure for predicting plasticity. First, the polarity of the predicted plasticity contributed by each pair of correlated pre- and postsynaptic spikes was determined from the time interval between them. Spike pairs with $20 > \Delta t > 0$ ms generated LTP, spike pairs with $0 > \Delta t > -75$ ms generated LTD, and spike pairs outside this window were ignored. Finally, for spike pairs within the LTP window, the magnitude of LTP was determined jointly by the membrane potential immediately preceding the postsynaptic spike and by the instantaneous frequency. (Adapted from Sjöström *et al.* (2001).) (*a*) Get sign from timing curve; (*b*) get amount of LTP from sigmoidal fit; (*c*) assume additional, linear frequency dependence for LTD; (*d*) amount of LTD is constant with frequency and depolarization. Hatching, LTP; shading, LTD.

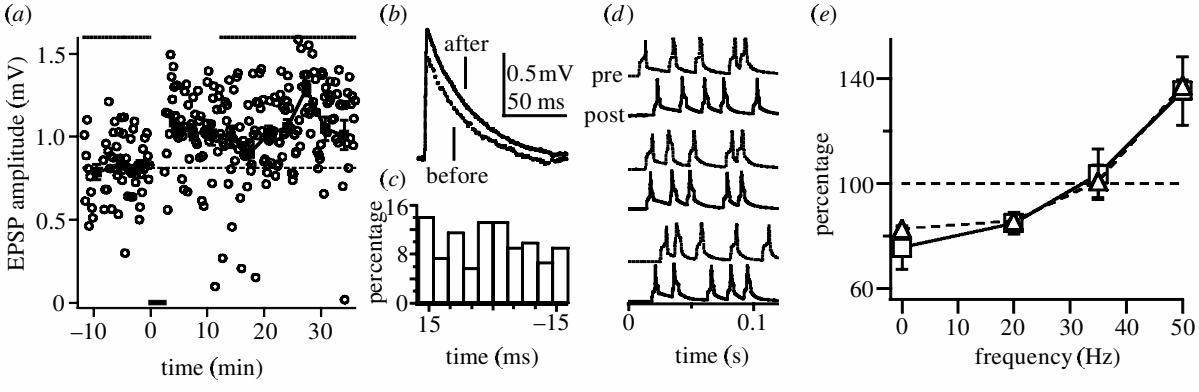

Figure 6. Quantitatively predicting the effect of random firing on synaptic plasticity. (*a*,*b*) Random firing at 50 Hz produced potentiation. The random spiking (three of 15 pairings) illustrated in (*d*) was equally distributed as pre-before-post and post-before-pre interactions (*c*), yet LTP was produced. (*e*) LTP (above 100%) or LTD (below 100%) are plotted as a function of the frequency of the random firing during induction. Other variants of the model in which, for example, all timing interactions were summed linearly did not fit as well. Squares, data; triangles, model, r.m.s. = 3.9; r.m.s. denotes root-mean-squared error (%) for the prediction of the model described in figures 4 and 5. (Adapted from Sjöström *et al.* (2001).)

Recently, Froemke & Dan (2002) have proposed an alternative model for how multiple pairs of pre- and postsynaptic spikes are integrated during induction of STDP. They indicated that when multiple interactions are present, the plasticity is dominated by the first interaction. In their model, each presynaptic spike reduces the efficacy of subsequent presynaptic spikes for causing plasticity. The efficacy recovers with a time constant of 34 ms. Similarly, postsynaptic spikes inhibit the efficacy of subsequent postsynaptic spikes and this recovers with a time constant of 75 ms. This model accurately accounts for the plasticity observed during extracellular stimulation experiments in which one or two presynaptic stimuli interact with one or two postsynaptic spikes (spike 'triplets' and 'quadruplets'). The effects they describe may reflect the need for a further refinement of the model presented here, or may reflect a difference between plasticity in layer 2/3 and layer 5. However, one difficulty of the Froemke and

Dan model is that it does not accurately predict the increase of LTP and the disappearance of LTD with increasing frequency. Instead, it predicts that the amount of LTP produced should be highest at low frequency, and should decrease with increasing frequency. In addition, it predicts that post-before-pre firing should produce LTD even at high frequencies. Further work will be required to determine whether a single model can account both for the spike 'triplet' and 'quadruplets' results and the frequency dependence found in our studies (Sjöström *et al.* 2001) and previously (Markram *et al.* 1997).

We found that our data were better fitted by a model in which only nearest-neighbour interactions between pre- and postsynaptic spikes were considered. As the LTD window is significantly longer (50–75 ms) than the LTP window (10–15 ms) this constraint has a much greater impact on the build-up of LTD. It is only at extremely high frequencies that multiple postsynaptic spikes can fall within 10–15 ms of a single presynaptic spike, but for LTD the overlap begins to occur above 20 Hz. Hence, the nearest-neighbour interactions could reflect a saturation of the signalling cascade underlying LTD.

The finding that the data were best fitted by a model in which LTP-promoting pre-before-post timings 'win out' over LTD-promoting post-before-pre timings is consistent with the observation that LTD disappears at high frequency (figure 3). Mechanistically, this could reflect the requirement for low levels of calcium influx to produce LTD, and the need for higher, more rapid levels to produce LTP (Lisman 1989; Artola *et al.* 1990; Yang *et al.* 1999). Once the level of calcium moves out of the LTD zone up into the LTP zone, no depression is produced, giving rise to an either/or relationship between LTD and LTP when combined over a short time-scale.

A challenge for future work will be to map the simple empirical model presented here onto more realistic biophysical models of LTP and LTD induction.

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GLOSSARY

AP: action potential
EPSP: excitatory postsynaptic potential
ISI: interspike interval
LTD: long-term depression
LTP: long-term potentiation
NMDA: *N*-methyl-D-aspartate
STDP: spike-timing dependent plasticity