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Contribution of Individual Spikes in Burst-Induced Long-Term Synaptic Modification

Robert C. Froemke,[1,2] Ishan A. Tsay,[3] Mohamad Raad,[1,2] John D. Long,[1,2] and Yang Dan[1,2,3]
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Froemke, Robert C., Ishan A. Tsay, Mohamad Raad, John D. Long, and Yang Dan. Contribution of individual spikes in burst-induced long-term synaptic modification. *J Neurophysiol* 95: 1620–1629, 2006. First published November 30, 2005; doi:10.1152/jn.00910.2005. Long-term synaptic modification depends on the relative timing of individual pre- and postsynaptic spikes, but the rules governing the effects of multispike bursts remain to be fully understood. In particular, some studies suggest that the spike timing dependence of synaptic modification breaks down with high-frequency bursts. In this study, we characterized the effects of pre- and postsynaptic bursts on long-term modification of layer 2/3 synapses in visual cortical slices from young rats. We found that, while pairing-induced synaptic modification depends on the burst frequency, this dependence can be explained in terms of the timing of individual pre- and postsynaptic spikes. Later spikes in each burst are less effective in synaptic modification, but spike efficacy is regulated differently in pre- and postsynaptic bursts. Presynaptically, spike efficacy is progressively weakened, in parallel with short-term synaptic depression. Postsynaptically, spike efficacy is suppressed to a lesser extent, and it depends on postsynaptic potassium channel activation. Such timing-dependent interaction among multiple spikes can account for synaptic modifications induced by a variety of spike trains, including the frequency-dependent transition from depression to potentiation induced by a postsynaptic burst preceding a presynaptic burst.

INTRODUCTION

Activity-dependent synaptic plasticity is crucial for shaping the structure and function of neural circuits. Recent studies have shown that repetitive pairing of pre- and postsynaptic spikes can induce either long-term potentiation (LTP) or long-term depression (LTD) of excitatory synapses, depending on the relative pre- and postsynaptic spike timing. If the presynaptic neuron fires within tens of milliseconds before the postsynaptic neuron (pre→post), LTP is induced (Bi and Poo 1998; Gustafsson et al. 1987; Levy and Steward 1983; Magee and Johnston 1997; Markram et al. 1997), whereas the reversed order of firing (post→pre) results in LTD (Bi and Poo 1998; Levy and Steward 1983; Markram et al. 1997). Such spike timing–dependent plasticity (STDP) has been observed at a wide variety of synapses in the vertebrate CNS (Boettiger and Doupe 2001; Debanne et al. 1998; Feldman 2000; Froemke and Dan 2002; Froemke et al. 2005; Nishiyama et al. 2000; Sjöström et al. 2001; Tzounopoulos et al. 2004; Wang et al. 2005; Zhang et al. 1998), and its functional consequences have been shown in vivo (Allen et al. 2003; Fu et al. 2002; Mehta et al. 2000; Schuett et al. 2001; Yao and Dan 2001; Yao et al. 2004). Theoretical studies have indicated that STDP is a powerful learning rule for solving a range of computational problems (Roberts 1999; Siegler et al. 2005; Song et al. 2000), such as learning of input sequences (Rao and Sejnowski 2001) and development of neuronal direction selectivity (Senn 2002) and cortical maps (Song and Abbott 2001).

Most experimental studies of STDP used simple spike patterns to induce synaptic modification. These experiments may not provide sufficient information for understanding how STDP operates in the intact brain, where spike trains often have complex temporal structures (Baddeley et al. 1997; Softky and Koch 1993). Early theoretical studies were based on the simplifying assumption that all pre/post spike pairs contribute independently to synaptic modification, and the effect of each pair depends only on its pre/post interspike interval (Kempter et al. 1999; Roberts 1999; Song et al. 2000; van Rossum et al. 2000). However, several recent experimental studies showed that synaptic modification depends on other properties of the spike trains in addition to the interval between each pre/post spike pair. In some studies, timing of the first spike (Boettiger and Doupe 2001; Froemke and Dan 2002) or the last spike (Wang et al. 2005) in each burst was found to be dominant in determining the sign and magnitude of synaptic modification. Other studies showed that synaptic modification is frequency dependent (Markram et al. 1997; Sjöström et al. 2001; Tzounopoulos et al. 2004) and that high-frequency bursts of pre- and postsynaptic spikes lead to LTP, regardless of the relative spike timing (Sjöström et al. 2001; Tzounopoulos et al. 2004). Although these studies all suggest the existence of additional rules for synaptic modification induced by complex spike trains, they have led to distinct phenomenological models.

In this study, we have further examined the effects of pre- and postsynaptic bursts in synaptic modification. In particular, we characterized the effects of individual spikes within each burst by systematically varying the frequency and number of spikes in both the pre- and postsynaptic bursts. We found that the frequency dependence of pairing-induced synaptic modification is a natural consequence of timing-dependent interactions among multiple spikes in the paired bursts. Furthermore, pharmacological experiments suggest that short-term depression of presynaptic transmitter release and the kinetics of postsynaptic action potentials during a burst can strongly affect the multispike interactions in the induction of spike timing–dependent long-term synaptic modification. These results provide important constraints not only for theoretical studies of the

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functional implications of STDP, but also for understanding the cellular mechanisms underlying this synaptic learning rule.

METHODS

Slice preparation

Acute slices of the visual cortex were prepared from 10- to 35-day-old Sprague-Dawley rats. Animals were deeply anesthetized with halothane and decapitated. The brain was rapidly placed in ice-cold dissection buffer containing (in mM) 206 sucrose, 2–2.5 KCl, 2 $MgSO_4$, 1.25 NaH_2PO_4, 1 $CaCl_2$, 1 $MgCl_2$, 26 $NaHCO_3$, and 10 dextrose, bubbled with 95% O_2-5% CO_2 (pH 7.4). Slices (300–400 μm thick) were prepared with a vibratome (Pelco), placed in warm dissection buffer (33–35°C) for <30 min and transferred to a holding chamber containing artificial cerebrospinal fluid (ACSF; in mM) 124 NaCl, 2–2.5 KCl, 1.5 $MgSO_4$, 1.25 NaH_2PO_4, 2.5 $CaCl_2$, 26 $NaHCO_3$, and 10 dextrose). Slices were kept at room temperature (22–24°C) for ≥1 h before use. For experiments, slices were transferred to the recording chamber and perfused (4.0–4.5 ml min^{-1}) with oxygenated ACSF at room temperature (for consistency with Froemke and Dan 2002; which is closely related to this). In some specified spike pair experiments (18 pre→post, 9 post→pre, triangles in Fig. 1*C*), ACSF contained 4 mM Mg^{2+}, 4 mM Ca^{2+}, and 3 μM bicuculline methiodide (Sigma) to reduce polysynaptic transmission and $GABA_A$ receptor–dependent inhibition. We found no significant difference in the amplitude or time window of STDP measured in these two solutions (Froemke and Dan 2002) and thus combined the data in our analysis.

Electrophysiology

Results from 335 experiments are included in this study, 100 of which have been reported previously (Froemke and Dan 2002). Somatic whole cell recordings were made from layer 2/3 (L2/3) pyramidal cells in current-clamp mode with an Axopatch 200B amplifier (Axon) using IR-DIC video microscopy (Olympus). L2/3 pyramidal cells were selected based on morphology and regular spiking patterns in response to current injection (Connors and Gutnick 1990). Patch pipettes (3–8 MΩ) were filled with intracellular solution (in mM): 120 K-gluconate, 10 HEPES, 0.1 EGTA, 20 KCl, 2 $MgCl_2$, 10 phosphocreatine, 2 ATP, and 0.25 GTP. The mean resting potential was –70.2 ± 10.5 (SD) mV, after correcting for the measured liquid junction potential of 6.8 mV. The mean series resistance (R_s) was 11.1 ± 8.7 MΩ, and the mean input resistance (R_i) was 121.9 ± 81.4 MΩ, determined by monitoring cells with hyperpolarizing current pulses (50 pA, 100 ms). Cells were excluded from analysis if R_i or R_s changed >30% over the entire experiment. Data were filtered at 2 kHz, digitized at 10 kHz, and analyzed with Clampfit 8 (Axon). Focal extracellular stimulation (0.01–1 ms, 5–150 μA) was applied in L2/3 with a small theta glass bipolar electrode 0.03–1.0 mm (but in most cases 0.1–0.2 mm) from the recording electrode. Stimulation strength was adjusted to evoke reliable excitatory postsynaptic potentials (EPSPs) of moderate amplitude (4.3 ± 2.7 mV). Stimulation frequency was maintained at 0.2 Hz throughout the experiment. The recorded EPSPs contain both mono- and polysynaptic components. The initial slope of EPSP (1st 2 ms) was used to measure synaptic strength, because this component reflects the early monosynaptic input to the cell (Feldman 2000). To test L2/3 pathway specificity, in some experiments, we placed a second stimulating electrode in L4 in the same column and monitored the evoked EPSPs. Paired-pulse

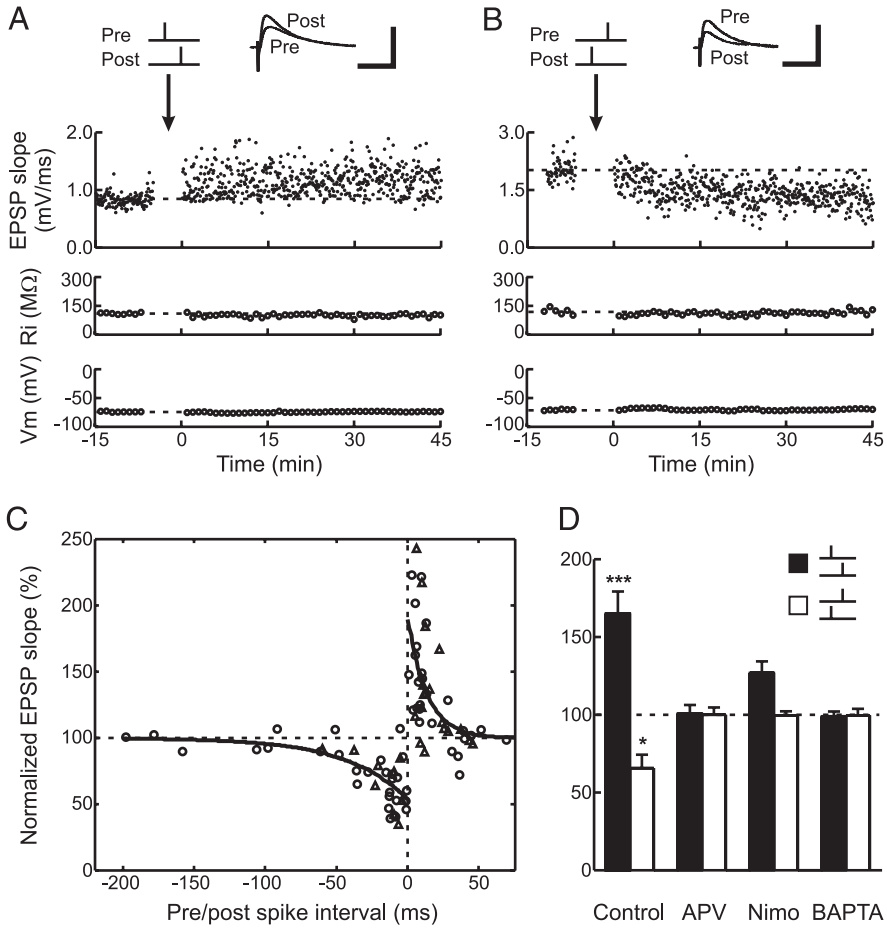

FIG. 1. Synaptic modification in cortical L2/3 induced by isolated pre/post spike pairs. *A*: example of long-term potentiation (LTP) induced by pre→post spiking (Δt = 10 ms, 60 pairs, Δw = 40.5%). Schematic above indicates the order of pre/post spiking repeated during the induction period (indicated by arrow). Sample traces show excitatory postsynaptic potentials (EPSPs) "pre" (mean of all EPSPs before induction) and "post" (mean of EPSPs from 11 to 20 min after induction) induction. Scale bars: 2 mV, 50 ms. Input resistance (*middle*) and membrane potential (*bottom*) were stable throughout the recording. *B*: example of long-term depression (LTD) induced by post→pre spiking (Δt = −10 ms, 80 pairs, Δw = −25.0%). Scale bars: 4 mV, 50 ms. *C*: dependence of synaptic modification on pre/post spike interval. Each symbol represents one experiment; circles, normal artifical cerebrospinal fluid (ACSF); triangles, high divalent ACSF with bicuculline. 32 of 45 pre→post and 24 of 38 post→pre experiments were reported previously in Froemke and Dan (2002). Curves, single exponential, least-square fits of the data. *D*: synaptic modification induced by pre/post spike pairing ($|\Delta t| \leq 7$ ms, averaged from experiments with 60, 80, and 100 spike pairs) in normal ACSF (control) and in the presence of pharmacological agents. Filled bars, pre→post spike pairing; open bars, post→pre pairing. Error bar: ±SE. n = 4–10. *$P < 0.05$; ***$P < 0.001$ compared with unpaired sham induction experiments. Compared with control, nimodipine significantly reduced LTP ($P < 0.01$).

depression was not observed across L2/3- and L4-evoked EPSPs, indicating independence of the two stimulation sites. Stable baselines of synaptic strength were established by 6–14 min of stimulation; cells were excluded if the mean EPSP slope was significantly different ($P < 0.05$, *t*-test) between consecutive minutes or between the first and the last minutes of the baseline period. During induction, postsynaptic spiking was evoked with depolarizing current pulses (0.5–2.5 nA, 1.5–5 ms); the minimum amount of current required to fire an action potential was used. Presynaptic spike timing was defined as the onset of the EPSP, and postsynaptic spike timing was measured at the peak of the action potential. The mean jitter in postsynaptic spike timing across the multiple trials in each induction protocol was 0.6 ± 0.5 ms. Synaptic strength after induction was measured 11–20 min after the end of the induction protocol. To determine significance of synaptic modification, we compared the magnitude of LTP or LTD induced after pre/post pairing to a set of one-spike "sham" control experiments; comparisons were made across groups using one-way ANOVA with a Bonferroni post hoc correction for multiple comparisons. In these experiments, during the induction period, either the postsynaptic cell did not spike ($n = 5$) or the postsynaptic cell fired in the absence of presynaptic stimulation ($n = 4$); no significant synaptic modification was induced in either case (presynaptic alone: $P > 0.25$; postsynaptic alone: $P > 0.45$ compared with the synaptic strength before induction).

Modeling

We consider three models of STDP for predicting synaptic modification induced by complex spike trains: the history-independent model, the original suppression model (Froemke and Dan 2002), and the revised suppression model.

HISTORY-INDEPENDENT MODEL. The contribution of each pre/post spike pair to synaptic modification was estimated as $\Delta w_{ij} = F(\Delta t_{ij})$, where w_{ij} is the change in synaptic weight induced by the *i*th presynaptic spike and the *j*th postsynaptic spike, and Δt_{ij} is the interval between the two spikes, $t_j - t_i$. The function F represents the time window for STDP measured with isolated pre/post spike pairs (Fig. 1*C*)

$$F(\Delta t) = \begin{cases} A_+ e^{-|\Delta t|/\tau_+} & \text{if } \Delta t > 0 \\ A_- e^{-|\Delta t|/\tau_-} & \text{if } \Delta t < 0 \end{cases}$$

A is the scaling factor and τ is the time constant, with + and – indicating pre→post and post→pre pairs, respectively. The net synaptic modification Δw was computed by combining the contributions of all pre/post pairs in the spike train, either additively or multiplicatively.

ORIGINAL SUPPRESSION MODEL. This model was similar to the history-independent model, except that the contribution of each pre/post spike pair to synaptic modification was estimated as $\Delta w_{ij} = \varepsilon_i^{pre} \varepsilon_j^{post} F(\Delta t_{ij})$, where ε_i^{pre} and ε_j^{post} are the efficacies of the *i*th presynaptic and *j*th postsynaptic spikes, respectively. For both pre- and postsynaptic spikes, $\varepsilon_k = 1 - e^{-(t_k - t_{k-1})/\tau_s}$, where t_k and t_{k-1} are timing of the *k*th and $(k-1)$th spikes of the neuron, respectively, and τ_s is the suppression time constant, obtained by fitting the data of the "2–1" ($n = 41$) and "1–2" ($n = 44$) experiments (for additive model, $\tau_s^{pre} = 35.0$ ms, $\tau_s^{post} = 78.0$ ms; these values are slightly different from those reported in Froemke and Dan 2002 because of additional "1–2" and "2–1" experiments). The history-independent model is therefore a special case of the suppression model, in which ε_i^{pre} and ε_j^{post} are always 1.

REVISED SUPPRESSION MODEL. The original suppression model was modified by altering the estimation of both pre- and postsynaptic spike efficacies. The efficacy of each presynaptic spike depends on the timing of all preceding spikes, rather than just the immediately preceding spike: $\varepsilon_i = \prod_{j=1}^{i-1} (1 - e^{-(t_i - t_{i-j})/\tau_s^{pre}})$, where $\tau_s^{pre} = 35.0$ ms, as in the original suppression model. For postsynaptic spike efficacy, the maximal suppression immediately after each postsynaptic spike was reduced: $\varepsilon_i = 1 - c e^{-(t_i - t_{i-1})/\tau_s^{post}}$, where c (an additional free parameter) and τ_s^{post} were chosen to minimize the root mean square (RMS) prediction error for the "1−n" experiments (for additive model, $c = 0.61$, $\tau_s^{post} = 198.0$ ms).

ADDITIVE VERSUS MULTIPLICATIVE MODELS. The effects of individual pre/post spike pairs in synaptic modification were combined using either the additive method ($\Delta w = \sum_{i,j} \Delta w_{ij}$, where Δw is net synaptic modification, and Δw_{ij} represents synaptic change caused by the *i*th presynaptic spike and the *j*th postsynaptic spike) or the multiplicative method ($[1 + \Delta w = \prod_{i,j}(1 + \Delta w_{ij})]$). When we compared the additive and multiplicative methods, which performed similarly in predicting the effects of natural spike trains in our previous study (Froemke and Dan 2002), we found that the prediction error of the additive method was lower than that of the multiplicative method for the "5–5" spike trains. We therefore used the additive method throughout this study.

SATURATION. The total amount of LTP induced by pre→post pairs and the total amount of LTD induced by post→pre pairs were calculated separately and were set to their respective saturation levels (65.3% for LTP and –34.2% for LTD, based on the measurements shown in Fig. 3*A*) if these levels were exceeded. Saturation was implemented for LTP and LTD separately before combining them, because several studies suggested that LTP and LTD are not simple reversal of each other; instead they are mediated by different cellular mechanisms (Montgomery and Madison 2004; Wang et al. 2005).

RESULTS

Synaptic modification induced by spike pairs

Whole cell recordings were made from L2/3 pyramidal neurons, and EPSPs were evoked at a low frequency (0.2 Hz) by extracellular stimulation in the same layer. In the first set of experiments, we extended an earlier study of these synapses (Froemke and Dan 2002) and measured the time window for STDP using a standard induction protocol, in which single-pulse presynaptic activation was paired with a single postsynaptic action potential at 0.2 Hz for 60–100 pairings (Bell et al. 1997; Boettiger and Doupe 2001; Feldman 2000; Froemke and Dan 2002; Froemke et al. 2005; Sjöström et al. 2001). Consistent with the previous study, we found that pre→post spike pairing at short intervals (Δt: 2–15 ms) induced LTP (Fig. 1*A*), whereas post→pre pairing (Δt: –2 to –15 ms) induced LTD (Fig. 1*B*). Figure 1*C* shows the change in synaptic strength as a function of the pre/post spike interval ($n = 83$). The pre→post ($n = 45$) and post→pre ($n = 38$) data were fitted separately with single exponential functions: $\Delta w = A e^{-|\Delta t|/\tau}$, where Δw is the percentage change in synaptic strength, Δt is the pre/post spike interval, and A and τ are free parameters. A and τ were found to be 89.5% and 13.5 ms, respectively, for $\Delta t > 0$ and –46.6% and 42.8 ms for $\Delta t < 0$.

Next, we assessed whether STDP depends on postsynaptic Ca^{2+} influx. Both LTP and LTD were abolished by either bath application of the *N*-methyl-D-asparate (NMDA) receptor antagonist D-APV or loading of the postsynaptic neuron with the high-affinity Ca^{2+} buffer BAPTA through the recording pi-

pette (Fig. 1*D*). Bath application of nimodipine, which blocks L-type voltage-dependent Ca^{2+} channels, reduced LTP and prevented LTD. Thus similar to the findings for hippocampal synapses and cortical L5 synapses, STDP of cortical L2/3 synapses depends on Ca^{2+} influx through NMDA receptors (Bi and Poo 1998; Debanne et al. 1994; Magee and Johnston 1997; Markram et al. 1997; Sjöström et al. 2001) and Ca^{2+} channels (Bi and Poo 1998; Debanne et al. 1994; Magee and Johnston 1997).

Synaptic modification induced by "5–5" trains

To examine the effects of spike bursts on synaptic modification, we first used "5–5" spike trains (Sjöström et al. 2001), each consisting of five presynaptic and five postsynaptic spikes at a certain frequency, with the postsynaptic train leading the presynaptic train by a short interval (6.0 ± 1.2 ms; Fig. 2*A*). Each "5–5 train was repeated 30–40 times at 0.2 Hz, and the spike frequency within the train (referred to as burst frequency)

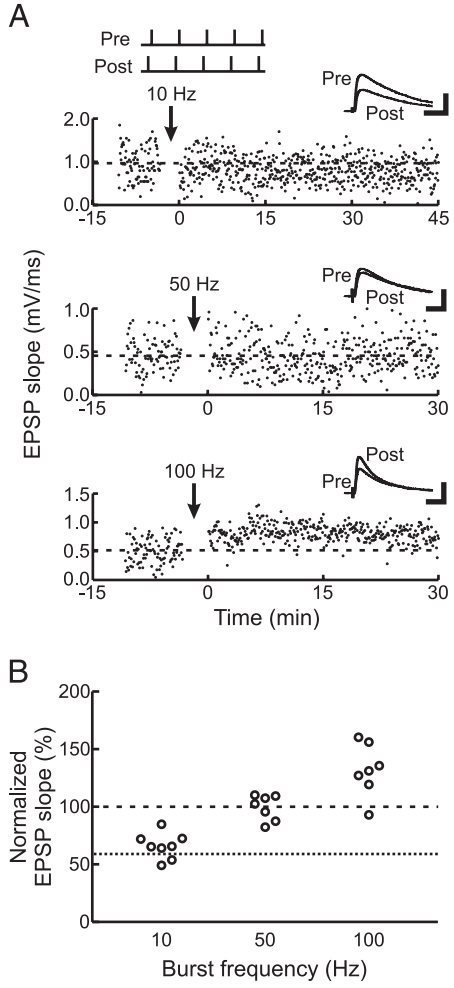

FIG. 2. Dependence of synaptic modifications on burst frequency. *A*: examples of synaptic modification induced by "5–5" spike trains with various burst frequencies. *Top*: 10 Hz, $\Delta w = -21.9\%$. *Middle*: 50 Hz, $\Delta w = -3.4\%$. *Bottom*: 100 Hz, $\Delta w = 60.4\%$. Scale bars: *top*, 4 mV, 40 ms; *middle*, 3 mV, 50 ms; *bottom*, 5 mV, 25 ms. *B*: summary of "5−5" spike train experiments with the 1st postsynaptic spike leading the 1st presynaptic spike by 6.0 ± 1.2 ms. Each circle represents 1 experiment. Dashed line, no change in synaptic strength; dotted line, mean synaptic modification induced by post→pre spike pairs with Δt between –2 and –15 ms (Fig. 1*D*, control).

was set at 10, 50, or 100 Hz. We found that synaptic modification depended significantly on the burst frequency, with LTD induced at 10 Hz but not at 50 Hz, and LTP induced at 100 Hz (Fig. 2). This is similar to the finding of Sjöström et al. (2001) for cortical L5 synapses and is consistent with their model in which LTP "wins over" LTD when the same spike participates in both pre→post and post→pre pairs with short interspike intervals. However, a simple suppression model for STDP at these L2/3 synapses, in which the efficacy of each spike in a burst is suppressed by its preceding spike (Froemke and Dan 2002), failed to predict the frequency-dependent transition from LTD to LTP. While this is not surprising, given that the natural spike trains used to test the suppression model contained relatively few high-frequency, multispike bursts, these bursts may nevertheless represent neuronal events of special significance (Reich et al. 2000; Reinagel et al. 1999). To define a more general rule that can account for synaptic modification induced by high-frequency bursts, we performed a series of experiments to determine the effects of the number, frequency, and relative timing of spikes in synaptic modification.

Saturation of synaptic modification

In the "5–5" induction protocol, the total number of spikes is much larger than that in the single spike pair protocol (Fig. 1). This might lead to saturation of LTP and/or LTD, which may play a prominent role in synaptic modification induced by these spike trains. We thus measured the dependence of LTP and LTD on the total number of spikes in the induction protocol, using single pre- and postsynaptic spikes paired at short intervals ($|\Delta t| \leq 15$ ms). We found that the magnitudes of both LTP and LTD increased with the number of pre→post pairs (Fig. 3*A*), but they saturated at ~60 pairs: there was no significant difference between the magnitudes of LTP induced by 60, 80, and 100 pre→post pairs ($P > 0.5$) or between LTD induced by 60, 80, and 100 post→pre pairs ($P > 0.6$). The saturation levels of LTP and LTD were thus determined by averaging the results at 60, 80, and 100 spike pairs with short pre/post intervals ($|\Delta t| \leq 7$ ms, which was used for the "5–5" experiments; 65.3% for LTP and –34.2% for LTD; Fig. 1*D*). We also noticed that, in some experiments, significant LTP was induced by ≤10 pre→post pairs, suggesting that these synapses are highly susceptible to the potentiation protocol.

To implement saturation, we first computed the net LTP induced by all pre→post pairs and the net LTD by all post→pre pairs separately by combining the effects of individual spike pairs additively (see METHODS). Then, the magnitudes of LTP and LTD were set at their respective saturation levels if these levels were exceeded. Finally, LTP and LTD were combined to predict the final change in synaptic strength. Compared with the original suppression model, which had an RMS error of 47.2% in predicting the mean synaptic modification at each frequency, implementing saturation reduced the prediction error to 26.5%, although it did not account for the transition from LTD to LTP at high burst frequencies.

Presynaptic bursts

Next, to determine whether the frequency dependence of synaptic modification observed in the "5–5" experiments reflects dependence on the presynaptic frequency, the postsyn-

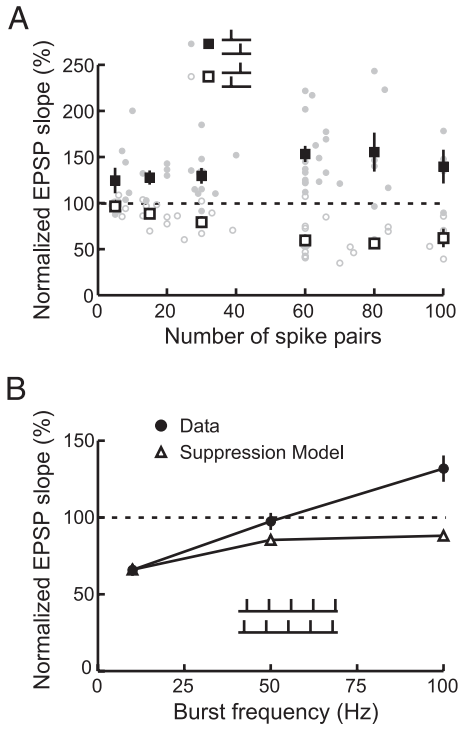

FIG. 3. Saturation of synaptic modifications. *A*: dependence of LTP and LTD on the number of pre/post spike pairs. Filled symbols, pre→post spike pairing (n = 50); open symbols, post→pre spike pairing (n = 38). Circles, individual experiments; squares, means ± SE. *B*: prediction of synaptic modification induced by "5–5" spike trains after saturation is incorporated into the suppression model. Filled circles, experimental data (same as in Fig. 2*B*); open triangles, additive suppression model.

aptic frequency, or a cooperative interaction between them, we examined the effects of pre- and postsynaptic spike bursts separately. To test the role of the presynaptic burst, we paired a burst of two to five presynaptic spikes at 100 Hz with a single postsynaptic spike that occurred either before (Fig. 4, *A* and *B*) or after (Fig. 4, *C* and *D*) the presynaptic burst ("n-1" spike trains, each repeated 30–40 times at 0.2 Hz). We found that a presynaptic burst following the postsynaptic spike by a short delay (≤6 ms) led to strong LTD, independent of the number of spikes in the burst (Fig. 4*B*). For these experiments, the suppression model also predicted maximal LTD at all spike numbers, which was determined simply by the saturation level.

In contrast to the result shown in Fig. 4, *A* and *B*, the same presynaptic bursts preceding the postsynaptic spike led to LTP (Fig. 4, *C* and *D*). This indicates that the order of pre- and postsynaptic spiking is crucial for synaptic modification even for high-frequency presynaptic bursts. Interestingly, increasing the number of presynaptic spikes led to a systematic reduction in the magnitude of LTP. Although the suppression model (Froemke and Dan 2002) predicted a monotonic decrease of LTP with the number of presynaptic spikes, the slope of decrease was underestimated (Fig. 4*D*). Note that, in this simple suppression model, the efficacy of each presynaptic spike depends only on its interval from the preceding spike (see METHODS). In the experimental data, the steeper decline of LTP with the number of presynaptic spikes suggests that the suppression of presynaptic spike efficacy should increase with successive spikes. We thus modified presynaptic suppression such that it accumulates over the entire presynaptic spiking history (see METHODS). Without any new parameters, this revised model accounted for the "$n-1$" experiments with a higher accuracy (Fig. 4*D*).

Mechanism of presynaptic suppression

The suppression of presynaptic spike efficacy in STDP (Fig. 4*D*) is reminiscent of short-term depression of transmitter release during high-frequency bursts (Tsodyks and Markram 1997; Varela et al. 1997). To examine the relationship between

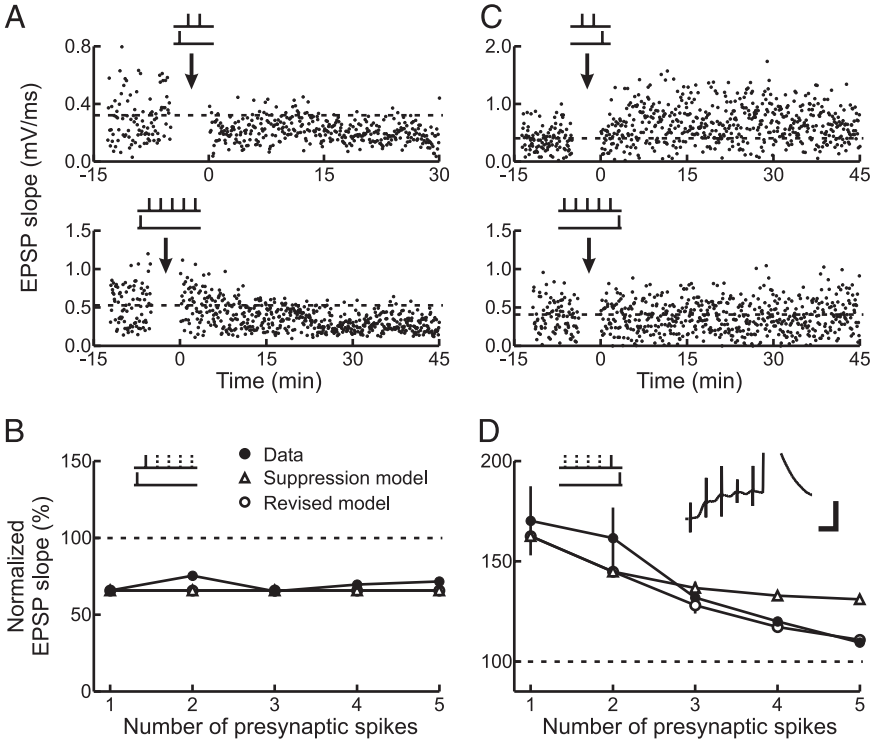

FIG. 4. Synaptic modification induced by "$n-1$" spike trains with a 100-Hz presynaptic burst. *A*: examples of synaptic modification induced by a presynaptic burst after a single postsynaptic spike. *Top*: "2–1" post→pre spike train, Δw = –18.6%. *Bottom*: "5–1" train, Δw = –31.7%. *B*: summary of synaptic modification induced by "$n-1$" post→pre spike trains. Error bars were smaller than symbol size. n = 3–8; 3 of 4 "2–1" experiments were reported in Froemke and Dan (2002). *C*: examples of synaptic modification induced by a presynaptic burst preceding a single postsynaptic spike. *Top*: "2–1" pre→post spike train, Δw = 75.5%. *Bottom*: "5–1" pre→post train, Δw = 2.1%. *D*: summary of synaptic modification induced by "$n-1$" pre→post spike trains. n = 3–8; 4 of 6 "2–1" experiments were reported in Froemke and Dan (2002). *Inset*: example induction trace from "5–1" experiment. Scale bar: 5 mV, 10 ms.

these phenomena, we first measured the time-course of paired-pulse depression (PPD) of the L2/3 synapses by evoking a pair of EPSPs with an interspike interval (ISI) between 5 and 1,000 ms (Fig. 5*A*). When we fitted the data with a single exponential $1 - e^{-t/\tau_{PPD}}$, the time constant τ_{PPD} was found to be 22.3 ms, comparable with the time constant of presynaptic suppression (35.0 ms). We tested whether manipulation of PPD can cause corresponding changes in interspike interactions in STDP. Because adenosine A1 receptors are known to regulate short-term synaptic plasticity by affecting the presynaptic transmitter release probability (Poncer and Malinow 2001; Varela et al. 1997), we examined both PPD and STDP in the presence of either 2-chloro-adenosine (Ado), an A1 receptor agonist, or 8-(*p*-sulfophenyl)-theophylline (SPT), an A1 receptor antagonist. While bath application of neither Ado (3 μM) nor SPT (20 μM) had obvious effects on the resting membrane potential, input resistance, or spike threshold, Ado converted PPD into paired-pulse facilitation (PPF; Fig. 5*A*, triangles) and SPT increased PPD significantly at short ISIs (squares). In experiments measuring long-term synaptic modification, we found that, while Ado and SPT did not significantly affect LTP induced by isolated pre→post spike pairs, they reduced and accelerated, respectively, the decline of LTP with the number of presynaptic spikes preceding the postsynaptic spike (Fig. 5*B*). Because the slope of this function directly reflects the degree of presynaptic suppression (Fig. 4*D*), these results are consistent with the hypothesis that interspike suppression of presynaptic spike efficacy in long-term synaptic modification is, at least in part, mediated by short-term synaptic depression. Of course, other factors, such as the progressive increase in the failures of presynaptic action potentials during the burst, may also contribute to presynaptic suppression.

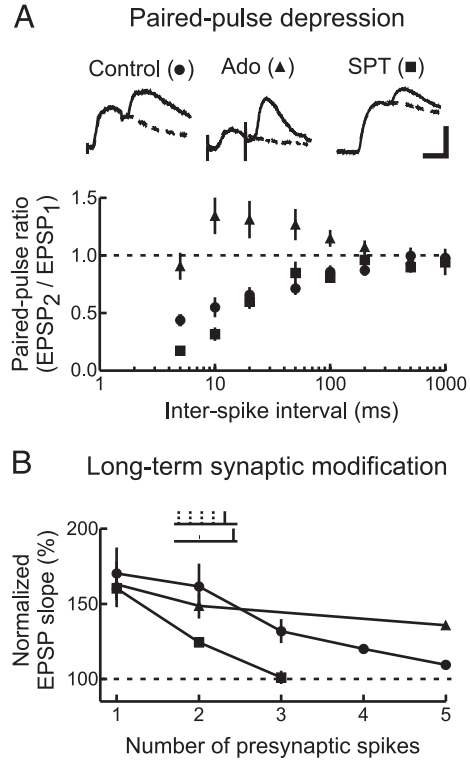

FIG. 5. Short-term depression and presynaptic suppression. *A*: paired-pulse ratio in normal ACSF (control) and with adenosine receptor agonist (3 μM Ado) and antagonist [20 μM SPT]. *Top*: example EPSPs evoked by a pair of presynaptic spikes [interstimulus interval (ISI): 20 ms]. Each trace is from a different cell. Solid lines, paired-pulse EPSPs; dashed lines, single EPSP. Scale bar: 3 mV; 10 ms. *Bottom*: time window of paired-pulse depression (PPD)/paired-pulse facilitation (PPF) for L2/3 synapses. Circles, PPD in control ACSF (n = 7–22). Triangles, PPD and PPF with Ado in the bath (n = 5–8). Squares, PPD with SPT in the bath (n = 4 to 6). *B*: synaptic modification induced by "$n-1$" pre→post spike trains in normal ACSF (same as in Fig. 4*D*) and with Ado or PPT in the bath.

Postsynaptic bursts

To understand how postsynaptic bursts affect synaptic modification, we paired a single presynaptic spike with two to five postsynaptic spikes (burst frequency: 100 Hz, each repeated 30–40 times at 0.2 Hz). As reported previously (Froemke and Dan 2002), we found that the post→pre→post spike pattern ("1–2" train) induced significant LTD (Fig. 6*A*). When more postsynaptic spikes were added before the presynaptic spike, LTD was still observed (Fig. 6*B*). While this result is qualitatively consistent with the suppression model, it is inconsistent with the model in which LTP "wins over" LTD. We also tested the effect of adding more postsynaptic spikes after the presynaptic spike and found it to cause a gradual shift toward LTP (Fig. 6, *C* and *D*). The distinct effects of the two "1–5" trains (Fig. 6, *B* and *C*) indicate that the relative pre/post spike timing is a crucial determinant of the direction of synaptic modification even with high-frequency postsynaptic bursts. While the original suppression model predicted a slight decrease of LTD with the number of postsynaptic spikes after the presynaptic spike, it failed to predict the transition to LTP with four or five postsynaptic spikes (Fig. 6*D*). This suggests that the efficacies of later spikes in the postsynaptic burst, which presumably contribute to LTP, are underestimated in the model. We therefore modified postsynaptic suppression, such that the efficacy of each spike is not reduced to zero immediately after the preceding spike (an assumption made in the original suppression model for simplicity, see METHODS), but instead drops to a value $1 - c$ (where $0 < c < 1$). Both the magnitude and the recovery time constant of suppression were obtained by fitting the model to the "$1-n$" experiments shown in Fig. 6*D* (c = 0.61, τ_i^{post} = 198 ms). After this modification of postsynaptic suppression, the model successfully predicted the transition from LTD to LTP with the increasing number of postsynaptic spikes (Fig. 6*D*).

Mechanism of postsynaptic suppression

A candidate mechanism for postsynaptic suppression in STDP is the frequency-dependent spike attenuation (Tanaka et al. 1991). To explore the relationship between the action potential kinetics and the suppression of postsynaptic spike efficacy, we blocked postsynaptic K^+ channels by intracellular loading of 4-aminopyridine (4-AP, 200 μM) through the recording pipette (Froemke et al. 2005; Hoffman et al. 1997). We found that 4-AP increased the amplitude and width of the spikes and abolished the attenuation of spike amplitude in high-frequency bursts (Fig. 7*A*). We measured long-term synaptic modification induced by a burst of postsynaptic spikes paired with a presynaptic spike, an experiment informative of postsynaptic interspike suppression (Fig. 6*D*). We found that, whereas 200 μM 4-AP did not significantly affect the magnitude of LTD induced by the "1–1" post→pre pairing at short

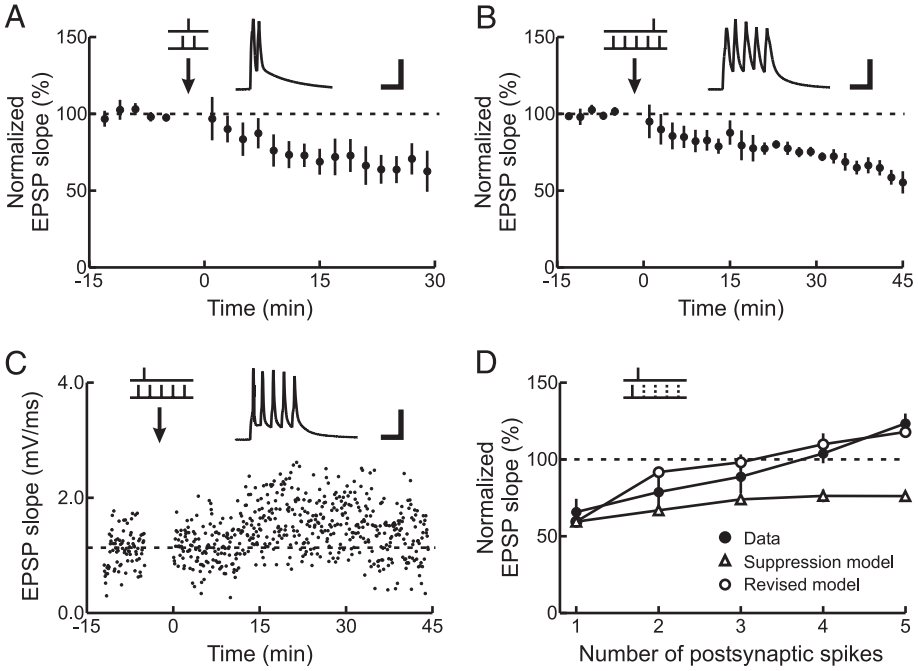

FIG. 6. Synaptic modification induced by "1−n" spike trains with 100-Hz postsynaptic burst. *A*: LTD induced by "1–2" spike trains ($\Delta w = -34.8 \pm 5.2\%$; $n = 13$, $P < 10^{-5}$), 6 of 13 "1–2" experiments were reported previously in Froemke and Dan (2002). *Inset*: example induction trace. Scale bar: 50 mV; 30 ms. *B*: LTD induced by "1–5" spike trains with 4 of the postsynaptic spikes preceding the presynaptic spike ($\Delta w = -19.3 \pm 6.8\%$; $n = 8$, $P < 0.03$). Scale bar: 50 mV; 20 ms. *C*: example of LTP induced by "1–5" spike train with 4 of the postsynaptic spikes after the presynaptic spike ($\Delta w = 38.5\%$). Scale bar: 50 mV; 20 ms. *D*: summary of synaptic modification induced by "1−n" spike trains with 4 of the postsynaptic spikes after the presynaptic spike. $n = 4$–12.

intervals, it markedly accelerated the transition from LTD to LTP with the increasing number of postsynaptic spikes (Fig. 7*B*, inverted triangles). This suggests that 4-AP enhanced the efficacies of later spikes in the postsynaptic burst, in parallel with its effect on postsynaptic spike attenuation (see DISCUSSION). In fact, the "1−n" experiments in the presence of 4-AP were better accounted for by the history-independent model (RMS error for the mean at each frequency: 9.8%) than by the suppression model (RMS error: 30.1%).

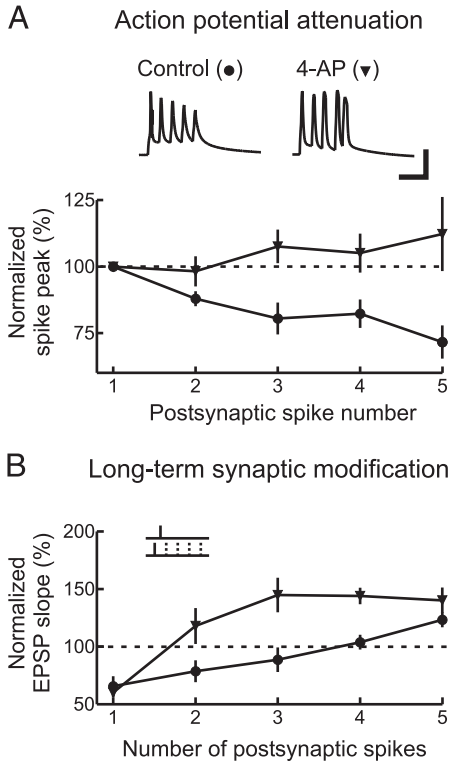

FIG. 7. Potassium channels and postsynaptic suppression. *A*: Spike attenuation with control intracellular solution and with 4-AP (200 μM) in the recording pipette. *Top*: example trains of 5 action potentials at 100 Hz. Each trace is from a different cell. Scale bar: 45 mV; 20 ms. *Bottom*: peak amplitude of action potential vs. spike number in a 100-Hz burst. $n = 4$–9. *B*: synaptic modification induced by "1−n" spike trains with 4 of the postsynaptic spikes after the presynaptic spike, with control intracellular solution (same as in Fig. 6*D*; circles) or with 4-AP in the recording pipette (inverted triangles). $n = 3$–4.

Evaluation of the revised suppression model

The efficacies of pre- and postsynaptic spikes in the 100 Hz "5–5" train according to the revised suppression model are shown in Fig. 8*A*. The presynaptic spike efficacy is strongly attenuated because of the accumulation of suppression at successive spikes, whereas the postsynaptic spike efficacy is less attenuated because of incomplete suppression immediately after the preceding spike. Note that interspike suppression generally causes an effective shortening of both the pre- and postsynaptic bursts in terms of their contributions to synaptic modification. An important feature of the revised model is that, at high frequencies, the presynaptic burst is more transient than the postsynaptic burst, so that even if the first postsynaptic spike precedes the first presynaptic spike, the net LTP induced by pre→post pairs may exceed the net LTD induced by post→pre pairs. As a result, the revised model accurately predicted the frequency-dependent transition from LTD to LTP induced by the "5–5" spike trains (Fig. 8*B*). When we compared the means of the predicted and the measured effects at each frequency, we found that the RMS error was only 1.1%.

To further evaluate the revised suppression model, we compared its performance to that of the history-independent model (efficacy of every spike is 1) and the original suppression model (efficacy drops to 0 immediately after the preceding spike and recovers exponentially) in predicting synaptic modification induced by a variety of complex spike trains. These data were from all the experiments ($n = 76$) not used for fitting the parameters of these models, i.e., "2–2" trains, "5–5" trains, and natural spike train fragments (most of the "2–2" and natural train experiments were from the previous

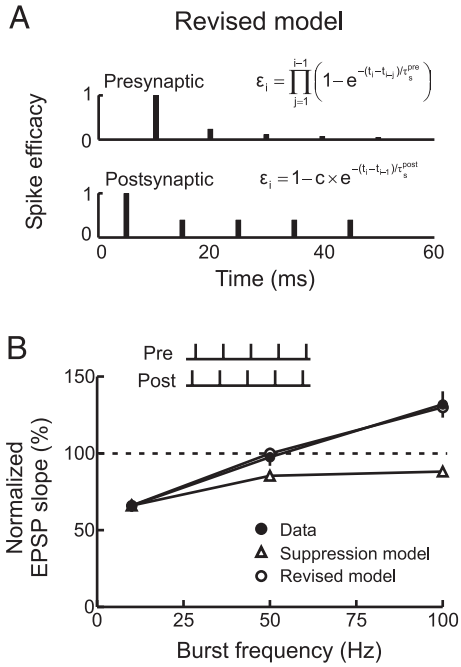

FIG. 8. Revised suppression model of spike-timing-dependent plasticity (STDP). *A*: efficacy of each pre- and postsynaptic spike in a 100-Hz "5–5" train, represented by height of each vertical line. *B*: prediction of synaptic modification induced by "5–5" trains by the original and the revised suppression models.

study, Froemke and Dan 2002). Because the main purpose of this comparison was to assess the effect of interspike suppression, we implemented saturation of LTP and LTD (Fig. 3*A*) in all three models. As shown in Table 1, whereas the modifications of the suppression model markedly improved the prediction of the "5–5" experiments, they did not significantly degrade the prediction of the "2–2" and natural spike train experiments. Over the 76 experiments, the RMS prediction error of the revised model was 20.0%, comparable with the RMS error of the single exponential fit to the pre/post spike pair experiments (Fig. 1*C*; 25.6%).

DISCUSSION

This study was directly prompted by the apparent breakdown of spike timing dependence of synaptic modification observed at high frequencies of paired pre- and postsynaptic bursts (Sjöström et al. 2001; Tzounopoulos et al. 2004; Fig. 2 of this study), which was not accounted for by the original suppression model for STDP (Froemke and Dan 2002). We found that, without appending separate rules for spike bursts, the suppression model can account for the experimental observations by incorporating three features: *1*) saturation of LTP and LTD; *2*) accumulation of presynaptic suppression over the entire spiking history of the cell; and *3*) reduced postsynaptic suppression immediately after the preceding spike. The revised suppression rule, which was still based on timing-dependent interactions among individual spikes, accounted for LTP induced by high-frequency post→pre bursts by making the presynaptic spike train effectively more transient than the postsynaptic spike train.

The main purpose of our model was to delineate an analytically tractable learning rule to facilitate theoretical exploration of the functional significance of STDP. It was therefore constructed to be as simple as possible, with a minimal number of free parameters to account for salient features of the experimental results. Although the revised model significantly outperformed the original suppression model in predicting the effects of high-frequency bursts in synaptic modification, there are quantitative differences between the model and the data (e.g., the slope of the function in Fig. 6*D* seems to be different between the model and the data). Because all the model parameters are based on experimental measurements at room temperature, their values are likely to be different in vivo at the higher physiological temperature. In addition, while this model is based solely on pre- and postsynaptic spike timing, other factors may also contribute to long-term synaptic modification.

TABLE 1. *Comparison of three models of STDP*

	Independent Model	Suppression Model	Revised Suppression Model
"5-5" trains (n = 22)	RMS: 23.1% Correlation: 0.57 R^2: 0.44 Correct sign: 17/22	RMS: 29.2% Correlation: 0.69 R^2: 0.11 Correct sign: 13/22	RMS: 13.4% Correlation: 0.79 R^2: 0.81 Correct sign: 19/22
"2-2" trains (n = 25)	RMS: 35.1% Correlation: 0.06 R^2: −0.33 Correct sign: 15/25	RMS: 19.6% Correlation: 0.68 R^2: 0.59 Correct sign: 21/25	RMS: 20.4% Correlation: 0.66 R^2: 0.55 Correct sign: 21/25
Natural trains (n = 29)	RMS: 41.0% Correlation: 0.18 R^2: −0.14 Correct sign: 16/29	RMS: 23.7% Correlation: 0.62 R^2: 0.62 Correct sign: 23/29	RMS: 23.6% Correlation: 0.68 R^2: 0.63 Correct sign: 23/29
All data (n = 76)	RMS: 34.7% Correlation: 0.25 R^2: −0.05 Correct sign: 48/76	RMS: 24.2% Correlation: 0.50 R^2: 0.49 Correct sign: 57/76	RMS: 20.0% Correlation: 0.69 R^2: 0.65 Correct sign: 63/76

Shown are four statistics: the RMS error, the correlation coefficient, R^2 ($R^2 = 1 - \Sigma e_i^2/\Sigma y_i^2$, where e_i is the error and y_i is the meas ured effect of the ith experiment), and the number of experiments in which the sign of synaptic modification (LTP or LTD) was correctly predicted. Comparisons are made for individual experiments between predicted vs. measured synaptic modification. Predictions are based on the additive versions of the history-independent model, the original suppression model, and the revised suppression model. Twenty-one of 25 "2-2" train and 22 of 29 natural spike train experiments were reported previously in Froemke and Dan (2002). STDP, spike timing–dependent plasticity; RMS, root mean square error; LTP, long-term potentiation; LTD, long-term depression.

For example, Sjöström et al. (2001) found that in cortical L5 neurons LTP depends on postsynaptic depolarization in addition to spiking, and this voltage dependence can help explain the dependence of LTP on burst frequency. In fact, previous studies showed that somatic spikes are not always necessary for the induction of LTP and LTD (Artola et al. 1990; Golding et al. 2002; Lisman and Spruston 2005) and our model does not account for these spike-independent forms of long-term synaptic modification. Finally, both the original and the revised suppression models predict that timing of the first spike in each burst plays an important role in synaptic modification, which is consistent with the finding in slices of songbird forebrain (Boettiger and Doupe 2001). However, this prediction may not be generally applicable to other synapses. In cultured hippocampal synapses, Wang et al. (2005) found that "2–1" trains (pre→post→pre) induced no synaptic modification, whereas "1–2" post→pre→post trains induced LTP. These findings are qualitatively different from both the original and the revised suppression models, which may be caused by differences in synaptic and intrinsic properties between hippocampal and neocortical neurons. There are also technical differences between these studies. All experiments in this study were carried out with extracellular stimulation, which evoke polysynaptic excitatory and inhibitory responses in the cortical circuit. With high-frequency stimulation, postsynaptic summation of the polysynaptic responses may play significant roles in long-term modification of the monosynaptic inputs.

Ultimately, a complete model can be constructed only by taking into consideration all the cellular events underlying long-term synaptic modification (Malenka and Bear 2004; Zucker 1999). Various mechanistic models have been constructed to explain the asymmetric window of STDP (Karmarkar and Buonomano 2002; Saudargiene et al. 2005; Senn et al. 2001; Shouval and Kalantzis 2005), and a recent model consisting of competing molecular modules for the induction of LTP and LTD (Rubin et al. 2005) has been used to account for the triplet experiments of Wang et al. (2005). The experiments shown in Figs. 5 and 7 represent our first attempts to explore the cellular mechanisms for the pre- and postsynaptic interspike suppression. It is important to note, however, that blocking K^+ channels and altering the action potential kinetics with 4-AP can affect the activation of postsynaptic voltage-gated ion channels, e.g., Ca^{2+} channels (Llinas 1988), which may also affect long-term synaptic modification. The effect of 4-AP on long-term synaptic modification may not reflect a direct relationship between spike attenuation and postsynaptic interspike suppression in STDP.

Theoretical studies have shown that interspike suppression in STDP facilitates development of direction selectivity (Senn 2002). It is also consistent with the prediction of an adaptive STDP learning rule designed to stabilize the firing rate of the postsynaptic neuron with changing presynaptic firing rates (Kepecs et al. 2002). In this study, experiments using high-frequency multispike bursts led to a revised suppression model, in which presynaptic suppression is much more severe than postsynaptic suppression. This suggests that, for the presynaptic spike burst, the onset time plays a dominant role (as subsequent spikes are less efficacious), whereas for the postsynaptic burst, both onset and offset times are important (as spikes throughout the burst contribute to net synaptic modification). This differential regulation of pre- and postsynaptic spike efficacy allows synchronous pre- and postsynaptic bursts at high frequencies to induce LTP even if the jitter in individual spike timing creates more post/pre pairing, which agrees with the well-established forms of rate-dependent plasticity (Malenka and Bear 2004; Zucker 1999). Thus interspike suppression, which may reflect basic properties of cortical synapses such as short-term depression, may help to ensure robust Hebbian strengthening of connections with coincident pre- and postsynaptic activity in the face of potentially noisy spike trains observed in vivo.

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