Timing and Contributions of Pre-Synaptic and Post-Synaptic Parameter Changes During Unitary Plasticity Events at CA3-CA1 Synapses

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KEY WORDS LTP; LTD; hippocampus; minimal stimulation; binary synapses

ABSTRACT At individual synapses, post-synaptic responses include a mixture of “successes” and “failures” in which transmitter is released or not released, respectively. Previously we measured synaptic strength at CA3-CA1 synapses averaged over all trials, including both successes and failures, using an induction protocol that allowed us to observe potentiation and depression events as step-like changes. Here we report quantal properties of 15 of the earlier experiments, including 14 potentiation events and eight depression events. In five experiments both potentiation events and depression events were evoked at the same synapse. During potentiation, success rate increased from 0.56 ± 0.14 (mean ± SD) to 0.69 ± 0.12, and during depression, success rate decreased from 0.70 ± 0.09 to 0.51 ± 0.10. During potentiation potency increased from 10 ± 5 to 19 ± 9 pA, and during depression, potency decreased from 18 ± 12 to 12 ± 7 pA. On average, changes in potency accounted for 76% of the change in response size in potentiation events and 60% of the change in depression events. A reduced-assumption spectral analysis method showed evidence for multiple quantal peaks in distributions of post-synaptic current amplitudes. Consistent with the observed changes in potency, estimated quantal size (Q) increased with potentiation and decreased with depression. A change in potency, which is thought to reflect post-synaptic expression mechanisms, was followed within seconds to minutes by a change in success rate, which is thought to reflect pre-synaptic expression mechanisms. Synaptic plasticity events may therefore consist of changes that occur on both sides of a synapse in a temporally coordinated fashion. Synapse 61:664–678, 2007.

INTRODUCTION
At individual hippocampal CA3-CA1 synapses, post-synaptic responses to a single pre-synaptic action potential are not reliable. Responses consist of a mixture of “successes” in which transmitter is released and detected and “failures” in which no response is recorded (Allen and Stevens, 1994). As a result, changes of strength, which occur on a variety of time scales in response to neural activity (Abbott and Regehr, 2004), can potentially be caused by a change in the probability that a successful event occurred, a change in the size of successful events, or a change in both at once. Distinguishing among these possibilities at CA3-CA1 synapses, a prevalent model system for studying synaptic plasticity, is a topic of experiment and lively debate.

The transmission properties of single CA3-CA1 synapses can be studied using the technique of minimal stimulation (Raastad, 1995). In minimal stimulation, during an intracellular recording from a CA1 pyramidal cell a stimulation electrode is used to activate pre-synaptic CA3 axons and the stimulus strength reduced until putatively only one axon contacting the CA1 neuron is activated. The hippocampal CA3-CA1

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synapse is favorable for minimal stimulation because the most commonly occurring number of morphological synapses between a CA3 and a CA1 cell is one (Sorra and Harris, 1993).

Using minimal stimulation at CA3-CA1 synapses, many investigators have studied changes in the distributional properties of unitary EPSCs resulting from two types of plasticity, long-term potentiation (LTP) and long-term depression (LTD) (Bekkers and Stevens, 1990; Isaac et al., 1996; Larkman et al., 1992; Stricker et al., 1996a). Evidence has accrued for both pre-synaptic (Bekkers and Stevens, 1990; Choi et al., 2000; Stevens and Wang, 1994) and post-synaptic (Hayashi et al., 2000; Isaac et al., 1996) changes occurring during long-term synaptic plasticity. These accounts have not yet reached consensus as to the relative importance of pre-synaptic and post-synaptic change, or even whether one or both changes occur (Bliss and Collingridge, 1993; Bliss et al., 2003). Another area of controversy (Korn and Faber, 1991) has been how to apply quantal analysis (Del Castillo and Katz, 1954) to central synapses, in particular whether separate peaks observed in response amplitude histograms can be interpreted as arising from the release of multiple quanta of neurotransmitter.

Here we report the analysis of a dataset of unitary excitatory post-synaptic current (EPSC) responses that were measured before, during, and after induction of LTP and LTD. The data were acquired for an earlier study in which we found that at putative single synapses, potentiation and depression occur in all-or-none, step-like changes (O’Connor et al., 2005). Our earlier study found that plasticity events are rapid, implying that the mechanisms underlying the initial expression of LTP and LTD are temporally well coordinated.

In the present study we separately analyze two parameters of synaptic transmission that relate to pre-synaptic and post-synaptic parameters. Pre-synaptic parameters are represented by the frequency of successes (success rate, SR) and failures. Post-synaptic parameters are represented by the response amplitude on successful trials (potency) or by another measure of responsiveness, the size of a single-quantum response (Q). We asked whether pre-synaptic and post-synaptic parameters both change during plasticity, and if so, whether they are synchronized with one another.

Although quantal analysis of CA3-CA1 synaptic plasticity is a frequently visited topic, our work is distinguished from other published studies in several ways. First, we examined whether the existence of quantal peaks could be extracted with fewer a priori assumptions regarding the nature of multiquantal release than many previous studies (see however Larkman et al., 1997; Stratford et al., 1997). Second, our data include both potentiation and depression events occurring in the same recording (see also Stevens and Wang, 1994), and we report the analysis of several cases in which single-synapse plasticity was induced and then reversed. Third, our induction protocols allowed us to resolve plasticity events as they occurred (O’Connor et al., 2005; Petersen et al., 1998).

MATERIALS AND METHODS

Analysis was done on a dataset of minimal synaptic currents acquired for an earlier study (O’Connor et al., 2005). Detailed methods of the preparation and electrophysiological recording can be found there. For the present study, data analysis and Monte Carlo simulations were performed in MATLAB with the Statistics and Curve Fitting Toolboxes. This dataset is available upon request.

Electrophysiology

Transverse hippocampal slices (300 μm) from Sprague-Dawley rats (P13-21) were prepared in accordance with procedures approved by the Princeton University Animal Care and Use Committee. After isoflurane anesthesia and decapitation, slices of the brain were cut in ice-cold artificial cerebrospinal fluid (ACSF) comprising (in mM) 126 NaCl, 3 KCl, 1 NaH2PO4, 25 NaHCO3, 2 CaCl2, and 1 MgCl2 saturated with 95% O2/5% CO2, incubated at 34°C for 10–15 min, and transferred to a room-temperature interface chamber for ≥60 min before recording. For recordings slices were transferred to an immersion-type recording chamber and perfused at 2–4 ml/min with ACSF at 23–26°C (14 experiments reported here) or at 34.5–35.5°C (three experiments reported here).

CA1 pyramidal neurons were recorded by blind conventional whole-cell or perforated patch recording and voltage-clamped to −70 mV. Patch pipettes (2–5 MΩ) were filled with (in mM) 133 methanesulfonic acid, 7.4 CsCl, 0.3 MgCl2, 10 NaHEPES, 0.2 EGTA, 3 Na2ATP, and 0.3 Na2GTP (pH 7.3 with CsOH, 290 mM). For perforated-patch recordings pipettes were tip-filled with pipette solution and backfilled with solution additionally containing up to 0.48 mg/ml amphotericin B and up to 0.16 mg/ml gramicidin D (Sigma). Series resistance for the experiments reported here was 32 ± 14 MΩ (mean ± SD). Experiments were rejected if series resistance changed by more than 30%. Liquid junction potentials were not corrected.

The stimulating electrode was an ACSF-filled pipette (2–5 MΩ), placed as far from the recording pipette as possible (limited by the surgical removal of CA3). Often the stimulation pipette had to be moved to several locations before minimal stimulation could be achieved. At each final location, a stimulus-response curve was obtained by systematically varying the stimulus current and recording the resulting EPSC amplitudes. Stimuli were given at 10–100 (mean 52) μA for a dura-
tion of 0.1 ms. Stimulation occurred at 1 Hz throughout recordings, a frequency that does not evoke short-term pre-synaptic enhancements in transmitter release and is not expected to lead to depression under post-synaptic voltage clamp at −70 mV (Christie et al., 1996). In all experiments, putative single-synapse responses were identified using the following criteria (Dobrunz and Stevens, 1997; Isaac et al., 1996; O’Connor et al., 2005; Raastad, 1995): (1) the mean amplitude and failure rate of responses were insensitive to changes of stimulus intensity of at least 10%; (2) decreasing the stimulus strength led to an abrupt and total failure of the response; (3) response latency did not change over the course of the experiment. 100 μM bicuculline or 10 μM bicuculline (Sigma) were included in the ACSF. For perforated patch recordings the ACSF included 0.5–1 mM glutamine (Sigma) to reduce the depletion of glutamate in presynaptic terminals (Larkman et al., 1991). LTP induction consisted of continued pre-synaptic stimulation and pairing every tenth stimulus with a depolarization to 0 mV, 40 times. LTD induction consisted of pairing every third stimulus with a depolarization to −55 mV, 130 times. Depolarizations lasted 700 ms and began 150 ms before the stimulus. We report EPSC sizes as the magnitude of the negative inward current.

Response size measurement and principal component analysis

From a total of 23 plasticity experiments and five control experiments, 15 experiments showing plasticity and two control experiments in which no protocol was given were selected that showed a clearly separate population of failures. These 17 experiments consisted of 16 perforated-patch recordings and one conventional whole-cell recording. During the 15 plasticity experiments a total of 14 potentiation events and eight depression events occurred. The 17 experiments yielded a total of 16,597 current traces for analysis. To remove stimulus artifacts, within each experiment from each raw EPSC current trace was subtracted the mean of 20–42 “failure” traces in which no response was detectable by visual inspection.

For principal component analysis (PCA), within each experiment the data were represented as the matrix

\[
Y = \begin{bmatrix}
y_1 - y^0 \\
y_2 - y^0 \\
\vdots \\
y_i - y^0 \\
y_n - y^0
\end{bmatrix},
\]

where \(y_i\) is the \(i\)th electrophysiology sweep of length \(m\) and \(y^0 = [y_1^0, y_2^0, \ldots, y_m^0]\) is a vector of the mean current for each of the \(m\) time points. The principal components were computed as the eigenvectors of the covariance matrix of \(Y\). To obtain the \(i\)th denoised EPSC sweep, \(s_i'\), we projected the \(i\)th row of \(Y\), \(s_i = y_i - y^0\), onto the first principal component \(p_1\) (that is, onto the eigenvector with the largest eigenvalue) and added back the mean currents, \(s_i' = (p_1 \cdot s_1)p_1 + y^0\). To obtain each final denoised time series observation we then took the peak of \(s_i'\). Overall the first principal component explained 90% ± 8% (mean ± SD across 17 experiments) of the variance in the raw data. Principal components were computed using not the whole current trace but rather a window covering part of the rising phase of the EPSC response and its peak. This window was of length 2–31 ms and was chosen within each experiment to give the best apparent separation of successes and failures, determined by visual inspection of the resulting time series of denoised EPSC amplitudes. To remove residual stimulus artifact and baseline offsets, in nine experiments the first four samples within the analysis window were mean-subtracted.

After projecting the data back onto the first principal component in some cases the failure responses were slightly offset from zero, reflecting the difficulty of completely removing baseline offset from each sweep. This offset was quantified by estimating the probability density of responses (as described later) and taking the mean of the failure peak as an offset. This offset, which ranged from 0 to 3.5 pA (mean 1.0 pA), was subtracted from the PCA-denoised amplitudes.

Data were segmented into before-plasticity and after-plasticity periods using the plasticity times determined previously. Briefly, breakpoints in the EPSC time series were found that minimized the sum of squares deviance, \(D\), defined as

\[
D(t) = \sum_{i=1}^{t} \left[ x_i - \frac{1}{t} \sum_{j=1}^{t} x_j \right]^2 + \sum_{i=t+1}^{n} \left( x_i - \frac{1}{n-t} \sum_{j=t+1}^{n} x_j \right)^2,
\]

where \(t = 1, 2, \ldots, n\) is the time of each possible breakpoint and \(x_i\) is the \(i\)th EPSC amplitude.

Because the earlier study included attempts to reverse or to saturate plasticity, LTP and LTD protocols in some cases continued throughout an experiment. When any of the data shown in a figure were acquired during an LTP or LTD protocol (or both), the time of protocol administration is indicated in the legend.

Estimation of probability densities

Kernel density estimation was used to calculate \(\hat{P}(x)\), a smoothed probability density of response amplitudes, from EPSC amplitude measurements.
\[ A = \{a_1, a_2, \ldots, a_i, \ldots, a_n\} \] (Stricker and Redman, 2003). The estimated density was defined as

\[
\hat{P}(x) = \frac{1}{n} \sum_{i=1}^{n} G(x - a_i \in A),
\]

where

\[
G(x) = \frac{1}{h \sqrt{2\pi}} \exp \left( -\frac{1}{2} \frac{x^2}{h^2} \right).
\]

Each density estimate \(\hat{P}(x)\) was defined at intervals of 0.1 pA spanning the range of A. The standard deviation, or bandwidth, of the Gaussian kernel, \(h\), used was \(h = f \times 0.9 n^{-1/5} \min(\sigma_A, IQR_A/1.34)\), where \(\sigma_A\) is the standard deviation of A and IQR_A is the interquartile range. \(f\) is an additional smoothing factor that varied depending on the purpose of the density estimation. For estimating EPSC densities, which are multimodal, we chose \(f = 1/5\) (Silverman, 1986), a value that gave \(h\) equal to 0.48 ± 0.24 pA (mean ± SD). Other values of \(f\) were used to estimate the envelope of a density prior to spectral analysis (\(f = 3/4\)), to smooth prior to automated detection of the failure peak (\(f = 1/2\)), and to get non-peaky densities for resampling for Monte Carlo simulations (\(f = 3/2\)). In each case we chose the minimum value of \(f\) that accomplished the goal of smoothing, as determined by our visual inspection of the smoothed density. For finding envelopes prior to spectral analysis, the goal of smoothing was to obtain a bimodal density showing only a failure mode and a success mode. We smoothed prior to detection of failure peak to remove random measurement noise prior to estimating a statistical parameter. Importantly, our results are not significantly altered by minor changes in the values of smoothing parameters.

**Estimation of SR, potency, failure peak, and quantal size**

Success rate, SR, was defined as two times the number of responses less than 0 pA (Gasparini et al., 2000; Isaac et al., 1996; Liao et al., 1995; Nicholls and Wallace, 1978). Potency, a measure of the size of the response on non-failure trials, was calculated by dividing the mean response amplitude by the SR. Except in the analysis shown in Figure 4, potency and SR were always computed using all the data prior to or all the data after a plasticity breakpoint.

As a second measure of successes/failures, the failure peak height of the response distribution was used. Using an over-smoothed EPSC amplitude probability density (\(f = 1/2\)), the location of the failure peak was defined as the local minimum (zero-crossing of the derivative) of this density within the amplitude range [-5 pA, 5 pA], or, if no local minimum was found, as the point of minimum derivative. The probability density value at the peak was reported in the figures and text as the failure peak height.

To estimate quantal size \(Q\), the over-smoothed density envelope \(\hat{P}(x)_{f=3/4}\) (\(f = 3/4\)) was subtracted from the EPSC probability density \(\hat{P}(x)\) to give residuals \(R(x) = \hat{P}(x) - \hat{P}(x)_{f=3/4}\) that eliminated low-frequency power unrelated to the spacing of quantal peaks. The power spectral density, \(PSD(\omega)\), of the residuals was computed by 2048-point FFT and then filtered with a 15-point moving average to give

\[
PSD'(\omega) = \frac{1}{2N + 1} \sum_{i=-N}^{N} PSD(\omega - i \delta\omega),
\]

where \(\delta\omega = 0.0049\) pA\(^{-1}\) and \(N = 7\), with truncation of the averaging window near endpoints. The quantal size was estimated as \(Q = 1/F_{max}\) where \(PSD'(F_{max}) = \max(PSD')\) and \(Q\) is in units of pA. For display in figures, power spectra were vertically rescaled to a maximum peak of 1.

**Monte Carlo simulations**

Monte Carlo simulations were performed to assess the probability that apparent quantal peaks in the EPSC densities could have arisen from a smooth parent distribution. One Monte Carlo simulation was carried out for each segment of EPSC data (i.e., before and after each plasticity event). For each segment of data, an over-smoothed version of the density, \(\hat{P}(x)_{f=3/2}\), was calculated to give a peak-free model distribution. One thousand random sets of \(N\) observations each were then drawn from \(\hat{P}(x)_{f=3/2}\), where \(N\) was the number of EPSCs in the original data segment. For each of these 1000 simulated data sets \(PSD'(F_{max}) = \max(PSD')\) was calculated to give a distribution corresponding to a peak-free model. The actual maximum power spectral density was then assigned a percentile score relative to the simulated data.

**Bootstrap error estimates**

Standard errors given in Table I for potency, SR and \(Q\) were computed using a bootstrap method. For each statistic, 1000 samples of \(N\) observations each were drawn with replacement from each segment of data, where \(N\) was the number of EPSCs in the original data segment. Potency, SR or \(Q\) was then computed on each of the 1000 samples, giving distributions for each re-sampled statistic. The standard error was then computed as the standard deviation of the re-sampled distribution.

**Statistical testing**

F-tests were used to test significance and calculate \(P\)-values for simple linear regressions in the figures.
### Table I - EPSC statistics and error estimates.

<table>
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<th>Cell</th>
<th>Event No.</th>
<th>No. Sweeps</th>
<th>Potency (pA)</th>
<th>SR</th>
<th>Mean amplitude (pA)</th>
<th>Q (pA)</th>
<th>No. Sweeps</th>
<th>Potency (pA)</th>
<th>SR</th>
<th>Mean amplitude (pA)</th>
<th>Q (pA)</th>
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<td>611</td>
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<td>514</td>
<td>11.6 ± 0.5</td>
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<td>14.9 ± 0.5</td>
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<td>530</td>
<td>3.7 ± 0.3</td>
<td>0.46 ± 0.04</td>
<td>1.7 ± 0.1</td>
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* 34.5° to 35.5° degrees C.  
* Omits paired (depolarized) sweeps, as well as the subsequent sweep if holding current was still returning to baseline.  
* Entry identical to that shown in immediately preceding 'After plasticity' section.  
* Gray highlights indicate events that failed the Monte Carlo test (see Results).  
* Error bars are the SEM determined by bootstrap (see Materials and Methods) and give a confidence interval.
and text. T-tests reported in the text on changes during plasticity were one-sample t-tests on the difference between values before and after plasticity. As appropriate, one-tailed tests or two-tailed tests were used.

RESULTS

A major aim of the present analysis was to measure changes in success/failure rate accurately. Therefore we denoised traces using PCA (Fig. 1A and B; Dityatev et al., 2003; Jolliffe, 2002). The trace amplitudes obtained using PCA matched the amplitudes of the original data (Fig. 1C; \( r^2 = 0.92 \pm 0.07 \), mean \( \pm \) SD across 17 experiments). However, the PCA-denoised EPSC amplitudes had a more pronounced separation of successes and failures (Fig. 1D). All analyses reported here are therefore based on the PCA-denoised data. For convenience we refer to the amplitude of each response projected onto the first principal component simply as the “EPSC amplitude.”

Estimation of SR and potency

We estimated quantal transmission parameters for each segment of data (Table I), where a segment was defined as all the data prior to or all the data after plasticity events identified by the deviance reduction method (O’Connor et al., 2005; see also Methods).
The first parameters we estimated were SR and response potency, using the method of doubling negative-amplitude responses (Gasparini et al., 2000; Isaac et al., 1996; Liao et al., 1995; Nicholls and Wallace, 1978). Because of recording noise, no single current trace can unambiguously be classified as a true success of transmitter release or a true failure. The negative-amplitude method avoids this problem by using the rationale that responses with negative amplitude are unlikely to be successful responses, and that unsuccessful responses, or failures, should be distributed evenly on either side of zero (in the region of gray in Fig. 1E). The SR is therefore defined as one minus twice the number of responses with negative amplitude (illustrated schematically in Fig. 1E). Potency is then defined as the mean response divided by the SR. Potency thus gives a measure of the response amplitude on success trials.

Estimation of quantal transmission parameters

The second approach to estimating quantal transmission parameters used the entire distribution of EPSC responses for each data segment to calculate quantal size and relative failure rate. We used kernel density estimation (Fig. 1F; see Methods) to estimate the probability densities from which the EPSC amplitudes were drawn (Malinow, 1991; Stricker and Redman, 2003). These densities showed apparently regularly spaced peaks, consistent with previous paired-recording and minimal stimulation data taken at this synapse (Dityatev et al., 2003; Foster and McNaughton, 1991; Kullmann and Nicoll, 1992; Larkman et al., 1991, 1997; Malinow, 1991; Sayer et al., 1989, 1990; Stratford et al., 1997; Stricker et al., 1996b; Stricker and Redman, 2003).

The presence of regularly spaced peaks has been interpreted as reflecting probabilistic release from multiple release sites (i.e., multiquantal release), where the spacing of the peaks reflects the quantal size, $Q$, the mean post-synaptic response to a single quantum of transmitter release. We used spectral analysis (Percival and Walden, 1993) of the amplitude distribution (Dityatev et al., 2003) to estimate $Q$ as the inverse of the frequency containing the most power (Fig. 1G). To estimate the relative failure rate we computed smoothed densities and then measured the first peak of the smoothed density, which reflects the distribution of failures (Fig. 1H; see Methods). These calculations of $Q$ and relative failure rate represent a means of estimating quantal parameters that are, to a degree, independent of the calculation of SR or potency.

An alternate interpretation of the peaks in our EPSC probability densities is that they might arise as a result of taking a finite number of measurements from an underlying amplitude distribution that is in fact smooth. To test this possibility we simulated data from smooth distributions. First, for each segment of EPSC data we computed a highly smoothed version of the probability density in which the quantal peaks were absent but the failure peak was still evident (Fig. 1I). This gave us a smooth model distribution resembling the observed distribution but without regular peaks. This method for generating smoothed distributions is based more directly on the data than fits to high-order polynomials (Dityatev et al., 2003) or unimodal distributions (Larkman et al., 1997). In particular unimodal fits do not reflect the fact that EPSC distributions with a significant number of failures must have at least two modes, one of the failures and one for the successes. We then sampled random amplitudes from the smoothed distribution one thousand times, each time taking as many observations as were in the original data segment being tested. Next we computed the power spectral density for each of these thousand samples in exactly the same way as was done for the original data segment.

The maximum value of the power spectral density for each of the thousand samples gave a measure of the amount of apparent periodicity observed by finitely sampling a smooth amplitude distribution. The null hypothesis was that peaks in our observed EPSC distributions were a sampling artifact, and therefore would not on an average be periodic. Thus, we histogrammed the maxima of the power spectra for all thousand samples taken from smooth distributions and compared with these the maximum obtained for the real EPSC distribution (Fig. 1J). We considered a plasticity event to “pass” this Monte Carlo test if either the segment of data prior to or the segment after the plasticity event scored at or above the 90th percentile of the re-sampled data. By this criterion, 7 of 14 potentiation events and four of eight depression events passed, for a total of 11 out of 22 events. This rate is significantly different from the chance expectation of 22 (1 − 0.90 × 0.90 = 4.2 events ($P = 0.001$). Thus a smooth distribution is insufficient to account for the observations, indicating the presence of regularly spaced true peaks in amplitude distributions.

Changes in both SR and potency during plasticity

We computed potency and SR for the entire periods prior to and after plasticity (Table 1). We found that both SR and potency changed during potentiation and depression, often in the same experiment (Figs. 2A–2D). Potency increased with potentiation from 10 ± 5 pA to 19 ± 9 pA ($n = 14$; $P = 9.38 \times 10^{-6}$, one-tailed $t$-test). Conversely, potency decreased with depression from 18 ± 12 pA to 12 ± 7 pA ($n = 8$; $P = 0.004$, one-tailed $t$-test). During potentiation, SR increased from 0.56 ± 0.14 (mean ± SD) to 0.69 ± 0.12 ($n = 14$; $P = 0.001$).
9.24 × 10⁻⁵, one-tailed $t$-test). Conversely, SR decreased with depression from 0.70 ± 0.09 to 0.51 ± 0.10 ($n = 8; P = 0.004$, one-tailed $t$-test). Across the population of plasticity events, changes in both SR and potency clearly segregated based on whether the event was a potentiation or a depression event (Figs. 2C and 2D), with potency and SR both increasing during potentiation and both decreasing during depression.

The shapes of probability distributions computed for EPSCs before and after plasticity showed changes consistent with both potency and SR changes. During potentiation, the peak of the distribution corresponding to failures decreased and the number of larger amplitude events increased (Fig. 2A, right). During depression, the number of large amplitude events decreased and the height of the failure peak increased (Fig. 2B, right). We quantified the change in failure peak and found that it decreased from 0.083 ± 0.037 (0.1 pA)⁻¹ to 0.052 ± 0.029 (0.1 pA)⁻¹ during potentiation ($n = 14, P = 0.02$, one-tailed $t$-test), and increased from 0.067 ± 0.047 (0.1 pA)⁻¹ to 0.100 ± 0.060 (0.1 pA)⁻¹ during depression ($n = 8; P =$
Across the population of plasticity events the effect was consistent, with a decrease in failure peak height during potentiation and an increase during depression (Fig. 2F). Changes in potency could reflect changes either in the number of quanta per successful response or in the size of a single-quantum response. Consistent with the latter possibility, we found that the quantal size estimate also increased during potentiation and decreased during depression (Fig. 2E). Analyzing only those experiments that passed the Monte Carlo simulation test (filled symbols in Fig. 2E; see Methods), we found that during potentiation, $Q$ increased from $3.9 \pm 2.3$ pA to $10.7 \pm 4.5$ pA ($n = 7$; $P = 0.0014$, one-tailed $t$-test). During depression, $Q$ decreased from $11.0 \pm 5.9$ pA to $4.9 \pm 2.0$ pA ($n = 4$; $P = 0.0527$, one-tailed $t$-test). Including the plasticity events that failed the Monte Carlo simulation test (hollow points in Fig. 2E) gave similar results: during potentiation, an increase from $3.6 \pm 2.3$ pA to $10.6 \pm 8.0$ pA ($n = 14$; $P = 0.0014$, one-tailed $t$-test); and during depression, a decrease from $10.1 \pm 5.8$ pA to $5.3 \pm 3.7$ pA ($n = 8$; $P = 0.0047$, one-tailed $t$-test). Our results support the expected association between initial potency and the contribution of potency to net plasticity. 

The fraction of total plasticity due to SR depends on the initial SR

We examined the relative contributions of potency and SR to the total change in mean response during potentiation and depression. We quantified the contribution of potency changes to changes in mean response size as $f_{\text{potency}} = \Delta \text{potency} / (\Delta \text{potency} + \Delta \text{SR})$, where $\Delta \text{potency} = (\text{potency}_{\text{post}} - \text{potency}_{\text{pre}})$ $\text{SR}_{\text{pre}}$ is the change due only to potency, and $\Delta \text{SR} = (\text{SR}_{\text{post}} - \text{SR}_{\text{pre}})$ $\text{potency}_{\text{pre}}$ is the change in pA due only to the observed change in SR. This quantity is the fraction of the total change due to a change in potency; values exceeding 100% correspond to cases in which SR moved in the opposite direction as net plasticity. During potentiation, the fraction of plasticity accounted for by an increase in potency (that is, $f_{\text{potency}}$) was $76 \pm 22\%$ (mean $\pm$ SD; $n = 14$), with a range of 27–104% (Fig. 3A). Conversely, during depression the fraction of plasticity due to a decrease in potency was $f_{\text{potency}} = 60 \pm 32\%$ (mean $\pm$ SD; range: 8–109%).

We found no relationship between $f_{\text{potency}}$ and initial potency (Figs. 3B and 3C; LTP: $r^2 = 0.09$, $P = 0.31$, $n = 14$; LTD: $r^2 = 0.04$, $P = 0.64$, $n = 8$). However, the large variability in $f_{\text{SR}}$, defined as $100\% - f_{\text{potency}}$ was correlated with the initial SR. In potentiation events, the fraction of plasticity accounted for by changes in SR...
decreased when the SR was initially high (Fig. 3D; 
$r^2 = 0.43, P = 0.011, n = 14$). Conversely, during 
depression the fraction of plasticity accounted for by 
a decrease in SR began already low (Fig. 3E; 
$r^2 = 0.49, P = 0.055, n = 8$), a result that 
was marginally significant in a direction consistent 
with the result for potentiation. In summary, most of 
the change in mean response could be accounted for 
changes in potency, with a remaining contribution 
whose size depended on the initial SR.

Changes in SR and potency are coordinated in time

The occurrence of plasticity events in all-or-none 
steps suggests that changes in SR and potency might 
occur in a coordinated fashion (Fig. 4). To compare 
the onset times of these events we made time series 
by binning the EPSC data into 10-s bins and calculating 
potency and SR for each bin. We then aligned the 
SR time series from all experiments by the optimal 
breakpoint in the corresponding potency time series 
(see Methods for definition of breakpoint). For both 
potentiation and depression, comparison of the two 
aligned time series revealed that both SR and potency 
changed at approximately the same time (Figs. 4C 
and 4D). Changes in potency were step-like (O’Connor 
et al., 2005). The time course of changes in SR (Fig. 
4D) were more difficult to resolve due to the smaller 
amplitude of changes in SR. Plotting the time courses 
of SR point-by-point against potency (Fig. 4E) revealed 
curved trajectories, indicating that the two 
quantities did not vary in tandem. Compared with a 
diagonal drawn from the baseline starting point at 
(1,1) to endpoints representing the steady-state values 
for depression and potentiation, the trajectories 
were curved downward for depression and upward for 
potentiation. This curvature suggests the possibility 
that for both potentiation and depression, changes in
SR start at approximately the same time as changes in potency but occur with a slower time course.

**Tests of the reversibility of changes in SR and potency**

We examined changes in SR and potency when plasticity was induced and then reversed at individual synapses (Fig. 5A). For each of the three periods of a plasticity reversal event (naive, after plasticity, and after reversal), we estimated SR, potency, and the EPSC probability density (Fig. 5). For SR, potency, quantal size, and failure rate, we calculated the fold change for each plasticity event (e.g., 1 → 2 or 2 → 3 in Fig. 5A) as the average parameter value in the potentiated state divided by the average parameter value in the depressed state. Although potency increased with potentiation and decreased with depression, the change was slightly larger during potentiation (Fig. 5D, left). The fold-change in potency with potentiation was 2.0 ± 0.5, significantly different from the fold-change during depression of 1.4 ± 0.3 (n = 7; P = 0.0003, two-tailed t-test). Conversely, SR increased with potentiation and decreased with depression, but changes were symmetric: the fold-change in SR with potentiation was 1.3 ± 0.3, vs. a change with depression of 1.6 ± 0.4 (n = 7; P = 0.12, two-tailed t-test). Asymmetry in reversibility was obscured in the overall mean response (SR × potency), in which the trends for SR and potency are in opposite directions and cancel each other (fold-changes of 2.5 ± 0.5 during potentiation and 2.2 ± 0.5 during depression; P = 0.20, two-tailed t-test). Thus, even though changes in mean response are similar in size for potentiation and depression events, potency changes in a more asymmetric fashion.

We also analyzed changes in quantal size and failure peak height. Across the seven reversal events, the change in quantal size was larger during potentiation than during depression (Fig. 5E, left). The fold-change in Q with potentiation was 4.1 ± 1.6, vs. a change with depression of 1.6 ± 0.4 (n = 7; P = 0.0080, two-tailed t-test). Asymmetry was also evident in the three reversal events that passed the Monte Carlo simulation test (see text). Other conventions as in D.
fold-change in Q of 3.9 ± 1.5 during potentiation and 1.8 ± 0.5 during depression. Reversal asymmetry was not evident in measurements of failure peak height (Fig. 5E, right). The fold-change in failure peak was 0.58 ± 0.13 with potentiation and 0.61 ± 0.17 with depression across all reversal events (n = 7; P = 0.75, two-tailed t-test). Taken together, results from both potency and quantal analysis indicate that on the time scale of these recordings, plasticity-induced changes in success/failure rates are reversible, while changes in potency and quantal size are partially irreversible.

**SR and potency do not strongly co-vary in magnitude or range of change**

The observation that both SR and potency increased during potentiation and both decreased during depression suggests that a synapse with strong potency might also have a high SR. In naïve synapses (synapses to which we had not yet delivered a plasticity protocol), there was some evidence for a weak relationship between initial SR and initial potency (Fig. 6A; \( r^2 = 0.24, P = 0.064, n = 15 \); potency log-transformed due to nonnormality of errors; rank correlation: Spearman’s \( \rho = 0.38, P = 0.17 \)). The weakness of this correlation raises the possibility that on long time scales, SR and potency are regulated independently to a degree.

Pre-synaptic and post-synaptic parameters might also be related in their capacity to change. We therefore looked for a relationship between the size of change in potency (expressed as a normalized or fold-change) and the size of change in SR. Within LTP and LTD groups the fold-change in SR and fold-change in potency were not correlated (LTP, \( r^2 = 0.14, P = 0.18 \); LTD, \( r^2 = 0.39, P = 0.10 \); Fig. 6B). Therefore not only SR and potency, but also the degree to which they can change, appear to be independently regulated.

**DISCUSSION**

We find that plasticity in unitary CA3-CA1 synaptic recordings is associated with temporally coordinated changes in SR and potency. SR and potency increased with potentiation and decreased with depression. Although the degree to which SR and potency contributed to the total net plasticity varied from experiment to experiment, in many cases a clear change was observed in both parameters. Our data thus support the many studies showing a change in both putative pre-synaptic and post-synaptic parameters (Hannay et al., 1993; Isaac et al., 1996; Kullmann and Nicoll, 1992; Larkman et al., 1992; Ryan et al., 1996; Stricker et al., 1996a).

We find that the onset of change in the pre-synaptic parameter is coordinated in time with change in the post-synaptic parameter. This coordination suggests that the triggers for changing SR and potency are mechanistically linked, since they occur at the same time. In prior work (O’Connor et al., 2005) we observed step-like changes in the mean EPSC during potentiation and depression. Here we have analyzed the time course of potency and SR separately. We found that potency occurs in step-like transitions, similar to the mean current (which equals SR × potency). This observation is consistent with the idea that exocytosis or endocytosis of a quantum of AMPA-receptors contributes to the step-like change in potency. SR was coordinated with potency in that both parameters began changing at approximately the same time, with an apparent lag in the onset of changes in SR. However, the SR was difficult to estimate, and we were unable to distinguish whether changes in SR were step-like or prolonged beyond a minute. Thus, even though pre-synaptic changes may be caused by post-synaptic events with a step-like character, it is unclear at this time whether the pre-synaptic changes are similarly sudden.

Because SR and potency are often thought to reflect largely presynaptic and post-synaptic processes, respectively, one explanation of our data is that plasticity events are communicated across the synapse. Among the possible mechanisms for retrograde signaling during plasticity in CA1 are post-synaptic release of a membrane-crossing signal, or release of neurotrophins (Bahr et al., 1997; Stäubli et al., 1998; Tao and Poo, 2001). Further, the synaptic cleft, which is 10–20 nm across, is filled with electron dense material, proteins. Pre- and post-synaptic membranes are in tight physical association, a situation that would allow fast direct signaling by membrane-bound factors such as cell adhesion molecules (Fitzsimonds and Poo, 1998; Lisman and Harris, 1993) and even gluta-
mate receptors themselves (Larkman and Jack, 1995). If the induction and initial expression of plasticity occur postsynaptically, the short delay to pre-synaptic expression could result from the action of either a diffusible retrograde signal or direct signaling by membrane-bound factors. Additional work will be required to elucidate both the kinetics and mechanisms of coordinated pre-synaptic and post-synaptic plasticity events.

It is important to note that while potency changes are often thought to arise from post-synaptic changes, for which much evidence has been reported (Nicol, 2003), potency is also determined by pre-synaptic factors such as the neurotransmitter content of individual synaptic vesicles (see for instance Karunanithi et al., 2002), and could change during synaptic plasticity. However, estimating changes in vesicle content requires fitting a much more complex model to the data than the relatively assumption-free method we have used here.

Our findings help point a way toward resolving apparent inconsistencies among a number of previous studies. We find that the magnitude of the contribution of SR to net plasticity depends on its starting value (see also Larkman et al., 1992; Larkman and Jack, 1995). This dependence on initial SR suggests one explanation for the inconsistent results from different studies with respect to changes in SR, with some studies showing large putative presynaptic changes (Bekkers and Stevens, 1990; Choi et al., 2000; Stevens and Wang, 1994) and others showing small if any evidence for SR changes (Foster and McNaughton, 1991).

In previous work the discovery of silent synapses in hippocampus has suggested a means of resolving conflicting results about the presynaptic vs. post-synaptic locus of LTP (Nicol, 2003). In the silent synapse model, an AMPA receptor silent synapse has NMDA receptors but no functional AMPA receptors. Upon LTP induction, functional AMPA receptors are recruited to the synapse, producing a larger post-synaptic response and an apparently lower failure rate, even though no change has occurred on the presynaptic side. Silent synapses are common in younger animals. Previous work (Xiao et al., 2004) indicates that synapses can be driven to silence in acutely prepared slices from neonatal animals (3–12 days), but not from older animals (29–32 days). In that work the age range we used (13–21 days) was not tested.

Three aspects of our data argue against de-silencing (and re-silencing) as causes of the changes we observe. First, in contrast to other studies, we have examined responses to both LTP and LTD protocols. SR is regulated bidirectionally, increasing with potentiation and decreasing with depression, in several cases at the same synapse. Second, Xiao et al. found that synapses from neonates were silenced by test pulse stimulation very rapidly after initiating the recording. In contrast, our perforated-patch recordings always included a long period of test pulse stimulation and establishment of minimal stimulation before applying an LTD protocol. Moreover, after depression our recordings always still showed EPSCs at ~70 mV. For this depression to be caused by synapse silencing would require that all recordings began with multiple non-silent synapses. Third, our recordings always started with measurable EPSCs and could always either potentiate or depress (O’Connor et al., 2005). A silent synapse account implies that in addition to multiple non-silent synapses, at least one silent synapse would also have to be present in each of these recordings. This explanation is unparsimonious. Thus it seems unlikely that our observed changes in SR can be explained by the presence of silent synapses.

Our finding that both SR and potency change during bidirectional plasticity is supported independently by our measurements of failure peak height and quantal size. Quantal size and failure peak are measures that do not depend on fitting a complex model to the data and make no specific assumptions about the statistics of release. More sophisticated models have allowed the estimation of additional parameters related to transmission, such as the mean number of quanta released, quantal content (Foster and McNaughton, 1991; Kullmann and Nicol, 1992; Larkman et al., 1992; Stricker et al., 1996a). However, the validity of detailed statistical models at central synapses is unknown (Korn and Faber, 1991), and plasticity may even change the statistical properties of release, for example from binomial to non-binomial (Stricker et al., 1996a). We have to a degree avoided these issues by estimating quantal size from the overall spacing properties of peaks in EPSC amplitude distributions. Many of our experiments showed peaky EPSC distributions, and our estimates of quantal size (~5 pA) are consistent with prior estimates.

Neurotransmitter release at CA3-CA1 synapses has been suggested to operate under the constraint that only one vesicle or quantum can be released at a time (Stevens and Wang, 1995). The multiple peaks in our EPSC distributions are more consistent with a multi-quantal release process. Our results are consistent with other studies that have provided evidence for multiquantal release by several technical approaches, including optical measurements (Conti and Lisman, 2003; Oertner et al., 2002) and a recent study using the low-affinity AMPAR antagonist γ-DGG under non-minimal stimulation conditions (Christie and Jahr, 2006).

One caveat to interpreting the peaks in our EPSC amplitude histograms is that it is possible that one or more putative unitary recordings was done from more than one synapse, despite the care taken to ensure stimulation of individual synapses (O’Connor et al., 2005).
Our mean EPSC potency is 13.1 pA prior to any plasticity, similar in amplitude to EPSCs measured with minimal stimulation at this synapse in prior studies from several research groups (Bekkers and Stevens, 1990; Dobrunz and Stevens, 1999; Isaac et al., 1996) and is within the range of currents (up to 30 pA) that can be elicited by two-photon glutamate uncaging onto single synapses of CA1 pyramidal cells in acute slices, under the same magnesium and calcium concentration conditions (see Supplemental Fig. 2 of Sobczyk et al., 2005). The few published CA3-CA1 paired recordings show smaller starting EPSC sizes (prior to plasticity, ~1–5 pA for voltage-clamp studies; Bolshakov and Siegelbaum, 1995; Malinov, 1991; ~0.03–0.7 mV for sharp intracellular microelectrode recordings; Friedlander et al., 1990; Sayer et al., 1989, 1990). These CA3-CA1 paired recordings might be less likely to exclude small-EPSC synapses. Conversely, establishment of minimal stimulation might select in favor of synapses with high signal-to-noise ratios, i.e., synapses with large EPSC amplitudes. We suggest that these two approaches-minimal stimulation and paired recording—both select for synaptic connections between individual CA3 and CA1 neurons, but may sample the population differently. Finally, we note that our experimental conditions deviated from physiological conditions in two respects. First, with the exception of three experiments, recordings were made at room temperature. Second, consistent with standard practice, extracellular calcium and magnesium concentrations were 2 and 1 mM, respectively, to reduce background activity in the brain slices.

We find that, during LTP, an increase in SR contributes less to net plasticity when the initial SR is already high, consistent with earlier observations by Jack and colleagues using different analysis methods (Hannay et al., 1993; Larkman et al., 1992). This result exemplifies a constraint in which the strength of a synaptic connection influences its ability to undergo potentiation or depression (Yang and Faber, 1991). Such a result would be expected if a parameter such as release probability could only move within a delimited range. In contrast, we found no relationship between the contribution of potency changes and the initial potency. This result can be explained if potentiation and depression occur in an all-or-none manner at this synapse, as we have shown previously (O’Connor et al., 2005). In this interpretation, our measurements of potentiation come entirely from synapses that are at minimum strength, and depression events come from synapses that are at maximum strength. Thus a synapse undergoing plasticity can move through its full range of potency, with no partial saturation. We do not therefore expect a relationship between initial potency and the contribution of potency to net plasticity.

Finally, although unitary strength transitions are all-or-none and saturating, our data indicate that synaptic change is more complex than a simple binary switch. We find that potency and quantal size changed by a slightly greater amount during potentiation than during depression. Previous analysis indicated that once plasticity is induced with an LTP or LTD protocol, it rapidly saturates such that further application of the protocol did not cause further plasticity (O’Connor et al., 2005). However, in that analysis the absolute levels (in units of pA) of similar saturated states were not exactly matched. One model consistent with our data is that on time scales of minutes, the induction of plasticity rapidly drives synapses to extremes, but on longer time scales, especially as a synapse is repeatedly “toggled” through potentiated and depressed states, the absolute levels of those extremes can vary.

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