Gain and fidelity of transmission patterns at cortical excitatory unitary synapses improve spike encoding

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Summary
Neuronal spike encoding and synaptic transmission in the brain need to be precise and reliable for well-organized behavior and cognition. Little is known about how a unitary synapse reliably transmits presynaptic sequential spikes and how multiple unitary synapses precisely drive their postsynaptic neurons to encode spikes. To address these questions, we investigated the dynamics of glutamatergic unitary synapses as well as their role in driving the encoding of cortical fast-spiking neurons. Synaptic transmission patterns randomly fluctuate among facilitation, depression and parallel over time. The postsynaptic calmodulin-signaling pathway enhances initial responses and converts this fluctuation to a synaptic depression. We integrated current pulses mathematically based on synaptic plasticity and found that they improve spike capacity and timing precision by shortening the spike refractory period at postsynaptic neurons. Our results indicate that the gain and fidelity of synaptic patterns enable reliable transmission of presynaptic signals by the synapse and precise encoding of spikes by postsynaptic neurons. These reproducible neural codes may be involved in controlling well-organized behavior.

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Key words: Unitary synapse, Synaptic plasticity, Interneuron, Action potential, Spike timing, Calcineurin, Ca2+-calmodulin.

Introduction
Elegant brain functions are controlled by neural signals precisely computerized at neurons and synapses in the central nervous system (Silberberg et al., 2005; Toledo-Rodriguez et al., 2005; Chen et al., 2006a; Chen et al., 2006b; Chen et al., 2006c). The establishment of well-organized behavior depends on experience-relevant plasticity in the functions of neurons and synapses (Kandel, 2000; Byrne, 2003). Long-term potentiation (LTP) (Bliss and Gardner-Medwin, 1973) and depression (Stanton and Sejnowski, 1989) of synaptic transmission are believed to be the cellular mechanisms for memory (Bliss and Lynch, 1988; Siegelbaum and Kandel, 1991). Well-organized behavior is thought to depend upon the stabilization of cellular functions, such as the uniformity of synapse dynamics, and the precise encoding of chronological spikes. It is not clear how transmission patterns at synapses are stabilized, how spike encoding at neurons becomes precise, or how their interaction produces reliable signals in neural networks for well-organized behavior.

Synapses are driven by sequential spikes generated at presynaptic neurons, which underlie frequency encoding (Shadlen and Newsome, 1994; Spruston et al., 1995; Koch, 1997; Fricker and Miles, 2001; Petersen et al., 2002). Although unitary synapses express either facilitation or depression in response to sequential spikes (Debanne et al., 1996; Reyes et al., 1998; Angulo et al., 1999; Reyes and Sakmann, 1999; Thomson and Bannister, 1999; Atzori et al., 2001; Rozov et al., 2001; Silberberg et al., 2005), the transmission patterns at these synapses randomly fluctuate among facilitation, depression and parallel (Wang and Wei, 2001). As synaptic patterns influence the encoding of postsynaptic neurons at any given time, their temporal fidelity is fundamentally important for stable communication between neurons and the encoding of precise signals in the neural network. It is not known how unitary synapses transmit chronological spikes reliably or how intracellular molecules modulate the accurate transmission of sequential spikes at central unitary synapses.

Neurons process sequential signals from a synapse and integrate numerous signals from hundreds of synapses. The current pulses integrated from these synapses encode spikes and drive membrane potentials toward thresholds (Spitzer et al., 2002; Daoudal and Debanne, 2003; Zhang and Linden, 2003; Somogyi and Klausberger, 2005). Spike capacity and timing precision are thought to be the parameters of neural computations (Shadlen and Newsome, 1994; Koch, 1997; London et al., 2002; Tiesinga and Toups, 2005; Chen et al., 2006a; Chen et al., 2006b; Chen et al., 2006c). Here, we address how the integration of events and plasticity from hundreds of synapses on a postsynaptic neuron quantitatively sets its excitatory state and spike encoding. The dynamics and modulation of glutamatergic unitary synapses from pyramidial to fast-spiking neurons were studied by dual whole-cell recordings in cortical slices. Synaptic signals from hundreds of inputs were analysed mathematically because it is difficult to study signal integration from numerous synapses experimentally. We also investigated the influence of integrated pulses on spike-timing precision and capacity in cortical fast-spiking neurons.

Results
Dynamic patterns of glutamatergic unitary synapses on fast-spiking neurons
We investigated the transmission patterns of unitary synapses in response to sequential presynaptic spikes, where ‘unitary’ refers to the connections from a neuron to another. Unitary excitatory postsynaptic currents (uEPSCs) were monitored by dual whole-cell
Facilitation and depression are not significantly different (P>0.05, Fig. 1B), displaying synaptic facilitation. A larger R1 was observed in 20 out of 39 synapses, which displayed synaptic depression (P<0.05, Fig. 1C,D). These two patterns are similar to those in previous reports (Debanne et al., 1996; Reyes et al., 1998; Angulo et al., 1999; Reyes and Sakmann, 1999; Thomson and Bannister, 1999; Atzori et al., 2001; Rozov et al., 2001; Wang and Zhang, 2004). Our data also show another transmission pattern at unitary synapses when R1 and R2 were not significantly different (n=7; Fig. 1E,F). Moreover, R1 and R2–R1 from those synapses were linearly correlated (Fig. 1G, r^2=0.7, P<0.05), indicating that synaptic patterns depend on the magnitude of initial responses at each synapse; larger responses are associated with depression and smaller responses with facilitation.

Three transmission patterns at unitary synapses are classified according to the averaged uEPSC amplitudes. However, the signal transmission at each glutamatergic synapse fluctuates temporarily among these three patterns. Fig. 2A,B shows data from a unitary synapse. The cumulative probability of uEPSCs in R2 is shown on the right; the mean values of R2 and R1 are 18.7±1.1 and 10.7±0.8 pA, respectively (mean ± s.e.m.; P<0.001; Fig. 2A). The plot of the difference between R2 and R1 vs time showed that most R2–R1 values were positive constantly; this dominant facilitation was associated with an irregular fluctuation among the three patterns in 40 minutes (Fig. 2B). Fig. 2C shows data from a unitary synapse where the cumulative probability of uEPSCs as well as the averaged R2 and R1 (16.7±0.7 and 29.9±0.9 pA, P<0.001) allowed synaptic depression. R2–R1 was not always negative and the dominant depression fluctuated irregularly (Fig. 2D). Fig. 2E shows a synaptic parallel at a unitary synapse where the cumulative probability for uEPSC1 and uESPC2 overlapped. The mean R1 and R2 were 11.5±0.25 and 11.1±0.24 pA (P=0.2). R2–R1 fluctuated evenly over 40 minutes (Fig. 2F). All cortical glutamatergic synapses fluctuated among facilitation, depression and parallel upon transmission of presynaptic spikes (50 msec intervals); however, all demonstrated one dominant pattern.

It is noteworthy that unitary synapses appear to have this fluctuating pattern in response to two presynaptic spikes with various intervals ranging from 20 to 150 msec (an example at 100 msec inter-spike interval (ISI) is illustrated in supplementary material Fig. S1). Analysis with fast Fourier transformation (see Materials and Methods) showed that the broad-frequency spectrum of synaptic fluctuation appeared to lack sharp-frequency peaks, suggesting that the fluctuation of transmission patterns at unitary synapses occurs in a chaotic manner.

**Postsynaptic Ca^{2+}-calmodulin signals influence synaptic patterns**

We hypothesized that the fluctuation in synaptic patterns is dynamically regulated by counterbalancing factors. These factors

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**Fig. 1.** Unitary synapses in response to presynaptic pair-spikes (50 msec intervals) express facilitation, depression and parallel patterns. (A) Paired presynaptic spikes (bottom trace) evoke a facilitation pattern of uEPSCs (top trace, R2>R1) at a unitary synapse (W-081200). (B) uEPSC amplitude is larger in R2 than R1 at each unitary synapse (P<0.05, n=12/39). (C) Spikes (bottom trace) evoke a depression pattern of uEPSCs (top trace, R2<R1) at a unitary synapse (W-070800). (D) uEPSC at R1 is larger than at R2 at unitary synapses (P<0.05, n=20/39). (E) Paired-spikes (bottom trace) evoke a parallel pattern of uEPSCs (top trace, R2=R1) at a unitary synapse (W-071203). (F) uEPSC at R2 equals that at R1 at each unitary synapse (P>0.05, n=7/39).

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**Fig. 2.** The transmission of presynaptic pair-spikes at unitary synapses that express facilitation, depression or parallel fluctuates among these three patterns in a chaotic manner. (A) The cumulative probability of uEPSCs shows that with a facilitation pattern, R2 (○) is larger than R1 (○). (B) Difference between R2 and R1 (R2–R1) plotted vs time. R2–R1 values fluctuate irregularly around the dotted line (zero). (C) A depression pattern produces uEPSCs with a cumulative probability of R2 (○) smaller than R1 (○). (D) R2-R1 values fluctuate widely around 0. (E) The cumulative probability of uEPSCs for R2 (○) and R1 (○) overlaps with a parallel response. (F) R2–R1 values fluctuate around zero irregularly. Data points above dotted line denote synaptic facilitation and those below the line denote depression.
Calcineurin autoinhibitory peptide (CaN-AIP) converts synaptic fluctuation into a depression pattern. The standard solution was filled in the tip of pipettes, and additional 40 μM CaN-AIP was back-filled. (A) R1 and R2–R1 values plotted against time. R1 increases (green symbols). The values of R2–R1 fluctuate across zero (dashed line), and remain below this line 30 minutes after CaN-AIP infusion (pink symbols). uEPSCs were sampled every 10 seconds. (B) Paired uEPSCs were sampled in the initial 4 minutes (control) and 30 minutes after the postsynaptic infusion of CaN-AIP. Correlation between R2–R1 and R1 in this unitary synapse plotted before (blue) and after (red) CaN-AIP infusion. CaN-AIP shifts synaptic fluctuation (blue) toward depression (red). (C) Paired uEPSCs in this unitary synapse are evoked by presynaptic spikes (bottom trace) before (blue) and after (red) CaN-AIP infusion. Calibration bars are 20 μs/160 pA for uEPSCs and 50 mV for spikes. (D) Other examples (n=9) showing that CaN-AIP converts synaptic fluctuation (thin lines) into depression (thick lines with same color), in which lines denote the correlation between R2–R1 and R1.

Calcineurin autoinhibitory peptide (CaN-AIP) enhances uEPSC1 and shifts the fluctuating synaptic pattern toward depression (Fig. 3A-D). An example is shown in Fig. 3A-C. The average amplitude of uEPSC1 was 41.87±3.75 pA in the initial 4 minutes and 35.29±3.3 and 35.95±2.9 pA before and after the infusion, respectively (P<0.81). Fig. 3A also shows a dynamic change in synaptic patterns during the infusion of CaN-AIP (pink symbols). R2–R1 values fluctuate across the zero line initially and swing toward synaptic depression after CaN-AIP infusion. The averaged R2–R1 values were –1.2±6.4 and –38.9±5.9 before and 35 minutes after the infusion (P<0.001), respectively. Moreover, R2–R1 vs R1 values were inversely correlated (Fig. 3B). Data points and a line showing their correlation over 0-4 minutes (blue) lay across the zero line, i.e. synaptic patterns fluctuate among facilitation, depression and parallel. At 35 minutes after CaN-AIP infusion (red), R2–R1 values fell, and the correlation line shifted towards negative values (depression) and to the right (R1 increase). Fig. 3D summarizes the data from other unitary synapses (n=9), where the inhibition of CaN activity converts the fluctuation of synaptic patterns (fine lines) into depression and enhances R1 (thick lines).

The inactivation of CaN facilitates protein phosphorylation (Wang and Kelly, 1997), which might lead to the conversion of synaptic patterns. To test this possibility, we infused Ca2+-CaM (40/10 μM) into postsynaptic neurons, which activates protein kinases (Wang and Kelly, 1995) and excludes the pulse-like activation of CaN. The results of an experiment infusing Ca2+-CaM is shown in Fig. 4A-C. The averaged values of uEPSC1 were...
Ca2+-CaM signaling pathways therefore upregulate synaptic strength. CaM enhanced uEPSC1 and converted the fluctuation of synaptic values (pink symbols) to depression after the infusion. The averaged values of R2–R1 were −133.6±14.0, respectively (P<0.0001). Fig. 4B shows that R1 increased and the fluctuated synaptic pattern shifted toward the depression after Ca2+-CaM infusion (red) compared with the initial 4 minutes (blue), where R2–R1 was inversely correlated with R1. Fig. 4D includes data from other unitary synapses, where Ca2+-CaM enhanced uEPSC1 and converted the fluctuation of synaptic pattern (fine lines) to depression (thick lines, n=5). Postsynaptic Ca2+-CaM signaling pathways therefore upregulate synaptic strength and convert transmission patterns toward depression at glutamatergic unitary synapses.

It is noteworthy that the conversion of the fluctuating synaptic patterns toward depression by postsynaptic Ca2+ signals is not specific for presynaptic ISIs of 50 ms. We found that infusions of CaN-AIP or BAPTA into postsynaptic fast-spiking neurons with 50-100 ms ISIs also converted the fluctuating synaptic patterns toward depression. An example of this during infusion of CaN-AIP (40 μM) with 100 msec ISI is shown in supplementary Fig. S1.

Next, we studied how the dynamics and plasticity of unitary synapses influence spike encoding at cortical fast-spiking neurons. A neuron receives hundreds of synaptic inputs (Freund and Buzsáki, 1996; Somogyi and Klausberger, 2005); and the dynamics vary among the synapses (see above). Little is known about how the signals integrated from these synapses with different transmission patterns and plasticity in a neuron influence spike programming. As it is difficult to simultaneously record hundreds of individual presynaptic inputs that are convergent onto a postsynaptic neuron, a compromise is to conduct the spatial and temporal integration of unitary events mathematically. After simulated integration based on our data above, we injected the integrated pulse currents into fast-spiking cells and examined their influence on spike programming.

Numerical integration based on the dynamics and plasticity of unitary synapses

During the integration, we took the dynamics of synapses, the number of active synapses and the synchrony of presynaptic inputs into account. Transmission patterns in response to two spikes at unitary synapses fluctuates among facilitation, depression and parallel randomly in the controls (Fig. 2), and such irregular fluctuation is converted into depression with the enhanced uEPSC1 by activating the CaM-signaling pathway (Figs 3, 4; Fig. 5B,C). This pathway also recruits active synapses from an inactive state, e.g. activation probability is raised to 0.81±0.07 from 0.23±0.04 (P<0.01, Fig. 5D,E) (see also Liao et al., 1995; Wang and Kelly, 2001; Wang and Zhang, 2004); this increases the number of active synapses.

In terms of the synchrony of presynaptic inputs, we assumed that the synapses on a postsynaptic neuron are activated asynchronously under control conditions based on the facts below. Threshold potentials to evoke spikes vary among cortical neurons (Chen et al., 2006a; Chen et al., 2006b; Chen et al., 2006c). This diversity may cause the asynchronous activation and propagation of action.
potential on presynaptic neurons such that spikes to their terminals activate synapses asynchronously. However, neuronal plasticity, in addition to lowering threshold (Zhang et al., 2004), is associated with the conversion of nonlinear-to-linear correlation \( r^2 = 0.23 \) and \( 0.71, P<0.01 \) between the threshold stimuli and the difference of threshold vs resting membrane potentials, as well being associated with an increase in linear slope from 12.5 to 29.2 (Fig. 5G). Increase in the efficiency of activating neurons allows them to activate synapses more synchronously.

With these data on the interval between inputs, the number of synapses and the plasticity of synaptic dynamics, we summated signals temporally and spatially from a population of excitatory unitary synapses, in which the parameters included the following.

1. The firing rate at presynaptic neurons was approximately 25 Hz. (2) They fired spikes asynchronously, i.e. inter-input intervals varied in the range 0.35-1.85 mseconds. (3) CaM strengthened uEPSC1 and converted the fluctuating synaptic pattern into depression. uEPSC1 and uEPSC2 both fell in the range 10-20 pA in controls, and were in the region of 20-40 and 10-20 pA, respectively upon CaM activation. (4) The number of synapses on a postsynaptic cell was assumed to be in the range of 50-400, which was raised by the conversion of inactive-to-active synapses (Fig. 5D,E). (5) The range in the synchrony of presynaptic inputs was narrowed (i.e. inter-input intervals altered from 0.6-1.6 to 0.5-1.0 mseconds) during neuronal plasticity (Fig. 5G).

The results in Fig. 6 show the quantitative summation of unitary synaptic inputs in the control (open symbols) and after CaM activation (filled symbols). The pulses in the control (Fig. 6A) were generated from 200 synapses that expressed facilitation, depression and parallel in the ratio 12:20:7 and where the presynaptic input intervals were in the range of 0.6-1.6 mseconds. The pulses under CaM activation (Fig. 6B) were generated from 300 synapses that expressed a depression pattern and where the presynaptic input intervals ranged from 0.5 to 1.0 mseconds, in addition to the other parameters listed in the previous paragraph. These integrated pulses are similar to ‘population’ EPSPs recorded intracellularly at the cortical neurons in vivo (data not shown). An increase in inter-input intervals caused the amplitude of integrated pulses to decay exponentially (Fig. 6C) and affected the duration of pulses in a linear manner \( r^2 = 0.99, P<0.001 \); Fig. 6D). The number of unitary synapses was proportionally correlated with the amplitude of pulses summed from fewer than 100 synapses (Fig. 6E), and was linearly correlated with the duration of the integrated pulses \( r^2 = 0.99, P<0.001 \); Fig. 6F). Note that the influence of the CaM signal on synaptic patterns and neuronal plasticity were taken into account in our simulation (filled symbols in Fig. 6).

### Influence of the integrated synaptic inputs on neuronal spike programming

To understand how the integration of excitatory unitary synapses influences the encoding of sequential spikes postsynaptically, we injected the integrated pulse-currents into cortical GABAergic cells from FVB-Tg(GadGFP)45704Swn/J mice (Fig. 5H). These neurons are fast spiking and have no adaptation, meaning that the calculation of mean spike capacity and timing precision is simplified. The use of this type of neuron is also consistent with fast-spiking neurons in our study of unitary synapses.

Fig. 7 illustrates spike patterns evoked by injecting the integrated pulses into fast-spiking neurons \( (n=14) \). The integrated input in Fig. 7A is the same as the control in Fig. 6A. This current pulse evokes sequential spikes with an unstable locking phase. When CaM was activated in postsynaptic cells (condition 2), inactive synapses became active and the fluctuation of synaptic patterns converted to a uniform pattern with enhanced uEPSC1 (Fig. 7B). An integrated pulse in Fig. 7B is similar to that in Fig. 6B, and its increase in amplitude and duration evoke more spikes. In addition, we integrated synaptic currents when the presynaptic inputs were activated synchronously, in which the range of inter-input intervals
changed from 0.6-1.6 to 0.5-1.0 mseconds (condition 3), which raised the amplitude of the integrated pulses (Fig. 6C and Fig. 7C). This pulse improved spike capacity and timing precision. These results indicate that the uniformity and enhancement of transmission patterns at excitatory unitary synapses and the presynaptic synchrony upregulate spike capacity and timing precision on the postsynaptic neurons.

This is also supported by quantitative data in Fig. 8. Spike capacity is denoted as ISI and spike-timing precision as the standard deviation of spike timing (SDST) (Chen et al., 2006a; Chen et al., 2006b; Chen et al., 2006c). Fig. 8A shows SDST for spikes 1-7 under the three conditions described above. The values of SDST1 to SDST4 are 2.12±0.31, 3.42±0.32, 5.18±0.78 and 7.95±1.57 mseconds in the control (open circles); the values of SDST1 to SDST4 are 1.41±0.19, 2.1±0.26, 2.66±0.35, 3.43±0.4, 4.78±0.7, 6.35±1.1 and 7.7±1.5 mseconds under condition 2 (gray); and the values of SDST1 to SDST4 are 0.7±0.1, 0.9±0.1, 1.33±0.1, 1.74±0.2, 2.1±0.25, 2.83±0.53 and 3.2±0.53 mseconds under condition 3 (black). SDST values for corresponding spikes among three conditions are statistically different (P<0.01). Fig. 8B illustrates ISI vs the number of spikes under the three conditions. The values of ISI1-2 to ISI1-4 are 45.99±2.18, 40.76±2.49, 41.85±2.7 and 39.89±2.14 mseconds in the control (open circles); the values of ISI1-2 to ISI1-4 are 22.61±2.31, 30.1±1.23, 29.02±1.2, 30.66±1.3, 33.36±1.68, 35.16±2.45 and 36.72±2.32 mseconds under condition 2 (gray); and the values of ISI1-2 to ISI1-4 are 15.6±0.74, 18.75±0.63, 18.89±0.8, 22.89±0.89, 23.59±0.84, 24.42±1.3 and 26.13±1.29 mseconds under condition 3 (black), respectively. ISI values for corresponding spikes between the three conditions are statistically different (P<0.01).

We further studied the mechanism underlying the improvement of spike programming caused by the plasticity of transmission patterns at excitatory unitary synapses. The data above suggest that larger integrated synaptic inputs are associated with better spike-timing precision and higher capacity. Because spike programming is essentially navigated by the refractory period (RP) of sequential spikes (Chen et al., 2006a; Chen et al., 2006b; Chen et al., 2006c), the improvement of spike programming during synaptic plasticity might be caused by larger integrated currents reducing the RP. We tested this hypothesis by measuring the absolute RP (ARP) of sequential spikes under different input intensities. Fig. 8C illustrates the measurement of ARP subsequent to spike 1 and spike 3 under weak stimuli (blue traces) and strong stimuli (red traces). The plot of the normalized stimulus intensity vs ARP for spike 1 (open symbols) and spike 3 (filled symbols) shows that these two parameters are inversely correlated in a linear manner (r^2=0.97 and r^2=0.96, Fig. 8D). The fact that stronger inputs are associated with a shorter ARP allows the improvement of spike programming by synaptic plasticity. It is noteworthy that absolute value for the linear slope of spike 3 (−10.4) is larger than that for spike 1 (−3.1); therefore, higher inputs more efficiently reduce ARP in the late phase of sequential spikes. This supports the fact that enhanced synaptic inputs mainly improve spike programming in its late phase (Fig. 8A).

Discussion
We analyzed the dynamics and plasticity of transmission pattern at glutamatergic unitary synapses as well as the influence of their integration on spike programming at cortical fast-spiking neurons. The transmission patterns at each synapse in response to presynaptic chronological spikes fluctuated among facilitation, depression and parallel randomly overtime. This fluctuation can be converted into a uniform synaptic depression by activating postsynaptic CaM signals. The pulses integrated from these uniform enhanced synaptic patterns upregulate the capacity and timing precision of sequential spikes by reducing their refractory periods. Our findings provide insight into how intracellular signaling pathways control the fidelity of unitary synapses to transmit sequential spikes, and how the plasticity of synaptic patterns influences spike encoding at neurons. The reliability of synaptic transmission and the precision of spike encoding are critically important to encode meaningful and memorable signals in neural networks that control well-organized

Fig. 7. The influence of the integrated currents from excitatory unitary synapses on spike programming at cortical GABA neurons. The rows from top to bottom are the integrated current pulses, spikes and spike timing; and columns A-C show spike patterns superimposed from 40 traces under three conditions. (A) Spike firing and timing evoked by a pulse similar to that in Fig. 6A (control). (B) Spike firing and timing evoked by a pulse that is simulated so that postsynaptic CaM converts inactive synapses into active ones. Fluctuating synaptic patterns were converted to a uniform pattern with an enhanced uEPSC1. (C) Spike firing and timing evoked by pulses that are simulated when presynaptic inputs are more synchronously activated (*, inter-input intervals changes from 0.6-1.6 to 0.5-1.0 mseconds). Such changes raise the amplitude of the integrated inputs, which improves spike capacity and timing precision.
behavior. Our study demonstrates how synapses and neurons interact for the precise computation of neural signals.

The physiological role of the plasticity of transmission pattern at unitary synapses

Transmission at each synapse, based on the averaged uEPSCs, show facilitation, depression or parallel patterns (Debanne et al., 1996; Reyes et al., 1998; Angulo et al., 1999; Reyes and Sakmann, 1999; Thomson and Bannister, 1999; Atzori et al., 2001; Rozov et al., 2001; Abbott and Regehr, 2004; Silberberg et al., 2005) (Fig. 1). In fact, each cortical glutamatergic synapse fluctuates among these three patterns irregularly in response to presynaptic sequential spikes (Fig. 2). The diversity and dynamic fluctuation of synaptic transmission patterns probably broaden the spectrum of neural codes that are available for complicated brain functions. However, because synaptic facilitation helps to drive the membrane potential toward thresholds, and synaptic depression has an opposite effect, an irregular fluctuation of transmission patterns forces the synapses forward presynaptic signals and drives the membrane potential toward the thresholds less predictably. In turn, postsynaptic neurons read synapse signals in a ‘confused’ manner and encode spikes in an unstable pattern, which is likely to be a cellular mechanism for the irregular behavior in animals before learning experiences establish transmission patterns.

In theory, transmission patterns at each synapse are necessarily disciplined for postsynaptic neurons to receive stable synaptic signals and to produce precise spike patterns. This is fundamentally important to stabilize the outputs of meaningful neuronal signals for well-organized behavior after physiological learning experiences. We found that the predominant activities of postsynaptic CaM-dependent protein kinases convert synaptic fluctuation into depression that is associated with the enhancement of an initial synaptic response (Figs 3, 4). The depression provides a dynamic gain-control for synaptic inputs onto a neuron (Abbott et al., 1997). The gain in response and depression pattern in the initial phase of synaptic inputs cause a rise in the synaptic integration that drives neuronal spiking. The reduced time window and a raised ability to activate neurons maximizes their spike encoding. Therefore, the fidelity and gain of synapse dynamics enhance and stabilize the ability of neurons to program sequential spikes (Fig. 8). Long-term stability of transmission patterns allows synapses to forward presynaptic spikes faithfully. Long-term stability of spike programming makes the neuronal output dedicated and precise. These disciplinary processes act like computer chips to ‘memorize’ the events in a linear pattern, and fit the cellular model of learning and memory.

Together, these results suggest that synapses and neurons are required to precisely and temporarily build up the meaningful neural codes that guide specific animal behavior. We propose that research of synaptic transmission patterns as well as neuronal encoding would be better focused on analyzing the temporal processes of synapses and neurons, rather than on the statistical average over time that is commonly studied.

Mechanisms underlying the transmission patterns of unitary synapses

The fact that inhibition of postsynaptic calcineurin shifts the fluctuating synaptic patterns into depression (Fig. 3) implies that a transient activation of calcineurin by Ca$^{2+}$ oscillation is involved in the fluctuation. This implication is strengthened by data suggesting (1) that the activation of postsynaptic CaM-dependent protein kinases converts the fluctuated synaptic patterns into depression (Fig. 4); (2) that Ca$^{2+}$-CaM attenuates synaptic facilitation (Wang and Kelly, 1996); and (3) that the paired pulses facilitate both Ca$^{2+}$ transient in spines and EPSCs (Emptage et al., 1999). With regards to synaptic fluctuation being postsynaptic in origin, the fact that unitary synapses at different cells express dominant facilitation, depression or parallel (Fig. 1) implies that the dynamic balance of signaling processes varies among postsynaptic neurons, which is consistent with the implication that synaptic patterns are target-cell specific (Reyes et al., 1998; Angulo et al., 1999; Reyes and Sakmann, 1999; Rozov et al., 2001). Thus, the postsynaptic mechanism is a primary set point for the transmission pattern for a given synapse.

The irregular fluctuation of synapse patterns is converted into synaptic depression by postsynaptic manipulation, but the fluctuation of R2–R1 values remain in depression (Figs 3, 4). This residual fluctuation may depend on presynaptic mechanisms that lead to short-term plasticity at the central synapse (Stevens and Wang, 1994; Wu and Saggau, 1994; Bolshakov and Siegelbaum, 1995) and peripheral synapse (Magleby, 1987; Zucker, 1989). Presynaptic factors include residual Ca$^{2+}$ (Katz and Miledi, 1968), release probability (Dobrunz and Stevens, 1997), asynchronous...
releases (Zucker and Regehr, 2002) and vesicle exocytosis styles (Zucker, 1996; Rettig and Neher, 2002). However, this residual fluctuation may be caused by the oscillation of a glutamate receptor (Glur) intrinsic property, because the burst, cluster and conductance levels of single Glur-channel activity vary over time (Cull-Candy and Usowicz, 1987).

Our view is different from the idea that presynaptic factors set synaptic patterns, which is based on studies of presynaptic sites (Zucker and Regehr, 2002). For instance, high presynaptic release probability is associated with synaptic depression and low probability with facilitation (Bolshakov and Siegelbaum, 1995; Dobrunz and Stevens, 1997). However, three synaptic patterns in our studies were observed in the sensory cortex, where synapses show a high probability of responsiveness (Atzori et al., 2001) (Figs 1-4). The release probability may not be the sole factor to set synaptic patterns. An alternative interpretation for the conversion of synaptic fluctuation to depression by postsynaptic manipulations is the participation of retrograde messengers (O'Dell et al., 1991).

Despite this possibility, our results propose that the postsynaptic mechanisms constitute a primary set point for the patterns of transmitting sequential spikes at glutamatergic synapses.

The fluctuation of synaptic transmission patterns in response to sequential spikes was observed by dual-recording of the kinetics of unitary synapses. However, a facilitation or depression without fluctuation was observed by activating population synapses (Manabe et al., 1993; Dumas and Foster, 1995) or using minimal stimuli (Stevens and Wang, 1995; Dobrunz and Stevens, 1997). The reasons for these differences need to be explored, because a complete understanding of such issues will tell us which configuration to record synaptic signals is more suitable for assessing synapse dynamics and plasticity. When injecting paired-current pulses into neurons, we observed that threshold stimuli are lower for spike 2 than spike 1 (data not shown). Pulse 2 in the extracellular stimuli may activate more axons when studying population synapses or applying minimal stimuli, such that synaptic facilitation with less fluctuation is seen. Therefore, synaptic dynamics and plasticity are better studied at the level of unitary synapses.

The plasticity of synaptic transmission patterns improves spike programming

A cortical neuron receives hundreds of synaptic inputs whose summation drives membrane potential toward the threshold potential to initiate spike (Koch, 1997; Spitzer et al., 2002; Zhang and Linden, 2003; Aymacher and Miles, 2004). Because both excitatory and inhibitory synapses terminate on the same neurons, the balance between them governs the drive toward thresholds and the encoding of spike patterns. Pulse-like depolarization currents (high variance inputs), which are generated by mixed excitatory and inhibitory inputs, improve spike-timing precision (Mainen and Sejnowski, 1995; Hess and Manira, 2001; Shu et al., 2003; Aymacher and Miles, 2004; Fellous et al., 2004; Person and Perkel, 2004). Sensory inputs and connections among the different cortical areas may be independent of inhibitory circuits. How do the integrated excitatory inputs affect spike programming? Studies show that the high frequency (Nowak et al., 1997) and the synchrony of excitatory synaptic inputs (Oviedo and Reyes, 2002) improve spike precision, and that the quanta events shape spike firings (Carter and Regehr, 2002).

Beyond these considerations, we investigated how the dynamics and plasticity of excitatory unitary synapses influence spike programming. The numerical integration of synaptic inputs, based on our data on the patterns of synaptic transmission, the number of synapses and the synchrony of presynaptic inputs (Fig. 5), was conducted under control conditions and plasticity (Fig. 6). This is a compromise to reveal how the dynamics of unitary synapses influences spike encoding, because it is impossible to individually record the hundreds of synaptic inputs that are convergent onto a postsynaptic neuron at the same time. Quantitative summation based on these factors produces step-style pulses that set the excitatory states of postsynaptic neurons at three levels. As step 2 varies under different conditions and mainly controls spike patterns, its amplitudes and duration vs inter-input intervals and synapse number were quantified (Fig. 6). CaM-induced uniformity of synaptic transmission patterns increased the amplitude of the integrated synaptic inputs.

We injected the integrated current pulses into cortical GABAergic neurons. Data analyses show that the uniform patterns of excitatory unitary synapses enhance spike capacity and spike-timing precision (Fig. 8A,B). In terms of the mechanisms underlying the improvement of spike programming, we found that the enhanced integration of synaptic inputs reduces the refractory periods of sequential spikes, which allows the increase in spike capacity and timing precision (Fig. 8C,D). These data provide an insight into the association between synaptic plasticity and neuronal spiking. Our data on the plasticity of transmission patterns at unitary synapses, the simulative integration of synaptic inputs and their influence on spike programming provide new avenues for quantitatively decoding neural signals at neurons and synapses.

The significance of improved spike programming by synaptic plasticity

The plasticity of synaptic transmission patterns improves spike-timing precision and capacity in the neuron (Fig. 8). High-frequency spikes induce synaptic plasticity in postsynaptic neurons (Bliss and Lynch, 1988). A good match of presynaptic vs postsynaptic spikes induces spike-timing-dependent synaptic plasticity (Sjostrom et al., 2001; Song et al., 2001; Dan and Poo, 2004; Tzounopoulos et al., 2004). Thus, the strengthened spike capacity and timing precision resulting from the plasticity of synaptic transmission patterns in these neurons will output high-frequency spikes and improve the pre/postsynaptic spike matching that induces synaptic plasticity on postsynaptic neurons. In this regard, our studies support the idea that plasticity at excitatory synapses improves spike-timing precision and capacity, which in turn facilitates the induction of plasticity at a subsequent grade of synapses in the neural network. The plasticity of synaptic transmission patterns and the improvement of neuronal spike programming interact to (1) strengthen the computation of neuronal signals and the efficiency of synaptic transmission in a chain reaction and (2) stabilize their activities for information storage.

Materials and Methods

Brain slices

Cortical slices (400 μm) were prepared from Sprague-Dawley rats or FVB-Tg(GadGFP)45704Swn/J mice whose GABAergic neurons expressed enhanced green fluorescent protein (eGFP). Rats or mice at postnatal day 14-20 were anesthetized with isofluorane and decapitated with a guillotine. Slices were cut with a vibratome fluorescent protein (eGFP). Rats or mice at postnatal day 14-20 were anesthetized with isofluorane and decapitated with a guillotine. Slices were cut with a vibratome.
submersion chamber (Warner RC-26G) that was perfused with normal ACSF at 31°C for the whole-cell recordings (Wang, 2003). The procedures were approved by IACUC in Beijing.

Neuron selection

Two synapse-coupled neurons in layer II-IV of the somatosensory cortex were recorded. Principal neurons have a pyramidal-like soma and apical dendrite, and interneurons are round with multipolar processes under DIC optics (Nikon FN-600). Pyramidal neurons and interneurons show different properties in response to hyper- and depolarization pulses (Wang and Kelly, 2001; Wang, 2003).

Dual whole-cell recording

Pair-spikes in the presynaptic pyramidal neurons were evoked by injecting depolarization pulses at 0.1 Hz. The pulse duration was 10 ms with an intensity to evoke a single spike for mono-peak uEPSC; and pair-spike intervals were 50 ms, which were outputted from an Axoclamp-2B amplifier in current-clamp model. uEPSCs were recorded under voltage-clamp at the soma of postsynaptic fast-spiking neurons (holding potential, −70 mV; Axopatch-1D) and inputted into pClamp 9 (Axon Instruments, Foster, CA) for data acquisition and analysis. Transient capacitance was compensated, and output bandwidth was 2 kHz for Axopatch-1D.

Instantaneous and state-steady currents evoked by 5 mV pulses (the first part of waveforms) were monitored in all experiments, which were applied to calculate series and input resistance. 10 μM CNQX was added to slices at the end of experiments to examine GluR-mediated uEPSCs.

Recording of spike patterns

Spike patterns in GABAergic interneurons that express eGFP were evoked by the simulated pulses under different conditions (control, synaptic plasticity and neuronal synchrony). The simulated pulses were converted into the ‘abf’ format for the interface with Clampex. Through an amplifier (Multi-clamp 700B), the simulated pulse currents were injected to evoke repetitive spikes, and signals were inputted into pClamp9 for data acquisition and analysis. Input resistance was compensated, and output bandwidth was 4 kHz.

Pipette solution and perfusion

The standard pipette solution contained 150 mM K-glutamate, 5 mM NaCl, 0.4 mM EGTA, 4 mM Mg-ATP, 0.5 mM Tris-GTP and 4 mM sodium phosphocreatine, 10 HEPES (pH 7.4 adjusted with 2 M KOH). Fresh pipette solution was filtered with a 0.1 μm centrifuge filter before use. The osmolality of pipette solution was 295-305 mosmol, and the resistance was >8 MΩ. Ca2+/CaM and Ca2+/CaM were dissolved in the distilled water for stock solutions that were 100 times higher than final concentration, and were diluted into the standard pipette solution before use. They were back-filled into uEPSC-recording pipettes whose tips were filled the standard solution. This allows recording under control conditions (initial few minutes) and subsequent molecule infusion (Wang and Kelly, 2001).

Analysis of uEPSCs

Electrophysiological signals were acquired by Digidata-1320A with pClamp 9. uEPSCs in response 1 (R1) and response 2 (R2) were measured by Clampfit if postsynaptic neurons exhibited the resting membrane potentials in the range –65 to −70 mV and there was no significant change in series and input resistances throughout the experiments. The indices of synaptic patterns include the cumulative probability and amplitude of uEPSCs, as well as the correlation between R2–R1 and R1. Data before and after the infusion of signaling molecules were compared using the Student’s t-test.

Analysis of temporal fluctuation in synaptic pattern

The frequency spectrum of R2–R1 was calculated with Fourier transformation:

$$P_\omega = \frac{1}{2\pi} \int e^{-i(\omega t)} dt,$$

where $P_\omega$ is the oscillation amplitude of harmonic mode with frequency $\omega$. $P_\omega$ plotted as a function of $\omega$ is the frequency spectrum. The Fast Fourier transformation (FFT) was used to calculate the frequency spectrum of the measured discrete data of R2–R1. Each peak in the frequency spectrum corresponds to the presence of an oscillation mode with frequency $\omega$ in the system. If a frequency spectrum calculated from R2–R1 consists of a few isolated peaks, the temporal fluctuation falls into a periodic state. However, a broad spectrum of frequency indicates a chaotic synaptic pattern or the stochastic dynamics of synaptic pattern. For a small set of data, the broad spectrum can only be seen if the dynamic system is completely random. Many non-sharpening peaks in the frequency spectrum suggest possible chaotic dynamics of the synaptic pattern. With this method, we analyzed the fluctuation of activity patterns at unitary synapses among facilitation, depression and parallel.

Simulation of pulse waves from the summation of synaptic inputs

To simulate the pulses summated from hundreds of presynaptic inputs that are activated randomly, we assume that presynaptic neurons ($p=1, 2, \ldots, N$) fire spikes at a specific rate, which evoke synaptic currents ($i$; i.e. uEPSCs) in a postsynaptic neuron at time $t_1, t_2, \ldots, t_N$. The summed input currents ($I$) can be described by

$$I(t) = \sum_{i} a_i(t-t_i).$$

(Rall, 1967). $a$ represents a single pulse that is impuned chronologically and decayed in a simply exponential manner. This is a simplified way for describing the characteristics of low-pass filter in synaptic transmission in that currents are required to rise rapidly. In reality, the rising and decaying phases of synaptic currents are slowly developed, and synapses are usually driven by two presynaptic spikes. Therefore, we should apply the following kernel for presenting two sequential synaptic responses:

$$\alpha_i = \frac{e^{-(t-t_i)/\tau}}{\tau},$$

in which $m$ and $n$ are the amplitudes of uEPSC1 and uEPSC2; and $\tau$ represents time constant. $\tau$ is the time interval of two pulses at a synapse, and $\Omega(t)$ is Heaviside step function with $\Omega(t)=1$ for $t>0$, and $\Omega(t)=0$ under other conditions.

The quantitative parameters used in the summation of currents from a population of glutamatergic unitary synapses are: (1) the firing rate ($F$) of presynaptic pyramidal cells is 25 Hz (Fig. 8), i.e. inter-spike intervals are 40 ms; (2) they fire spikes asynchronously so that inter-input intervals are 0.35-1.85 ms; (3) CaM signals enhance uEPSC1, and convert the fluctuated transmission pattern at unitary synapse into depression. The amplitudes of uEPSC1 vs uEPSC2 are 10-20 vs 10-20 pA in the controls, and 40-40 vs 10-20 pA under CaM activation; (4) the number of synapses on a postsynaptic neuron ranges presumably from 50 to 400, which can be upregulated by a conversion of inactive synapse to active one (Fig. 5D-E). (2) The spectrum in the synchronous of presynaptic synapses is narrowed during the plasticity (Fig. 5G), from 0.6-1.6 to 0.5-1.0 mseconds, which allows synaptic convergence more synchronously. The simulation was done using a self-produced program in Mat-lab.

Chemicals

6-Cyano-7-nitroquinoxaline-2,3-(1H,4H)-dione (CNQX) was supplied by Sigma. Calcineurin autoinhibitory peptide and calmodulin were from CalBiochem. Other chemicals were from Fisher Scientific.

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