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Differential Effects of Excitatory and Inhibitory Plasticity on Synaptically Driven Neuronal Input-Output Functions

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SUMMARY

Ultimately, whether or not a neuron produces a spike determines its contribution to local computations. In response to brief stimuli the probability a neuron will fire can be described by its input-output function, which depends on the net balance and timing of excitatory and inhibitory currents. While excitatory and inhibitory synapses are plastic, most studies examine plasticity of subthreshold events. Thus, the effects of concerted regulation of excitatory and inhibitory synaptic strength on neuronal input-output functions are not well understood. Here, theoretical analyses reveal that excitatory synaptic strength controls the threshold of the neuronal input-output function, while inhibitory plasticity alters the threshold and gain. Experimentally, changes in the balance of excitation and inhibition in CA1 pyramidal neurons also altered their input-output function as predicted by the model. These results support the existence of two functional modes of plasticity that can be used to optimize information processing: threshold and gain plasticity.

INTRODUCTION

A large number of studies have characterized the mechanisms and learning rules underlying synaptic plasticity, and it is generally accepted that changes in synaptic strength contribute to learning and memory (Martin et al., 2000; Malenka and Bear, 2004). However, since alterations in behavior must ultimately be caused by changes in neuronal firing, it is not synaptic plasticity per se, but how synaptic plasticity modifies the *output* of neurons, that underlies learning. Thus, to understand the relationship between synaptic plasticity and learning it is important to elucidate how synaptic plasticity alters the input-output characteristics of neurons.

We use the term *neuronal input-output (I/O) function* to refer to the relationship between the excitatory input to a neuron and the probability it will generate an action potential (Figures 1B and 1C; Daoudal and Debanne, 2003; Staff and Spruston, 2003; Marder and Buonomano, 2004; Campanac and Debanne, 2008). A neuron's I/O curve, generally represented as a sigmoidal function, is characterized by two components: the threshold and the gain. Here, we define the I/O threshold as the EPSP slope that elicits a spike 50% of the time (this usage is similar to that in the artificial neural network literature in which threshold refers to the midpoint of the activation function; Rumelhart et al., 1986). The gain refers to the rate of change or sensitivity of the I/O function (Figure 1C). The I/O threshold and gain of a neuron are directly related to its computational role, as both of these features can be used to quantify the ability of neurons to discriminate sensory stimuli (Mountcastle and Powell, 1959; Maffei and Fiorentini, 1973; Dean et al., 2005) and optimize the encoding of sensory information (Laughlin, 1981). Indeed, at the psychophysical level similar measures are used to quantify behavioral performance, where the threshold and gain are related to the point of subjective equality and just noticeable difference, respectively (Morrone et al., 2005; Lapid et al., 2008).

Previous studies have established that LTP alters the threshold of the I/O function—a phenomenon referred to as EPSP-spike (E-S) potentiation (Andersen et al., 1980). Specifically, an EPSP of the same strength (as measured by the slope), that was not effective in eliciting spikes, can fire the cell after the induction of LTP. While the mechanisms underlying the LTP-induced shift in the I/O function continue to be debated (Daoudal and Debanne, 2003; Frick et al., 2004; Marder and Buonomano, 2004; Campanac and Debanne, 2008), the balance of excitation and inhibition is known to be an important contributing factor. For example, one reason that an EPSP of a given size can elicit a spike after LTP, but not before, is due to an increase in the excitation/inhibition ratio. After LTP, a smaller stimulation intensity is required to elicit the same size EPSP, and consequently fewer inhibitory neurons will be recruited and those that are will have a longer latency, which facilitates the generation of the action potential (Marder and Buonomano, 2004). However, in contrast to the threshold, previous studies have not examined how excitatory plasticity influences the gain of neuronal I/O functions.

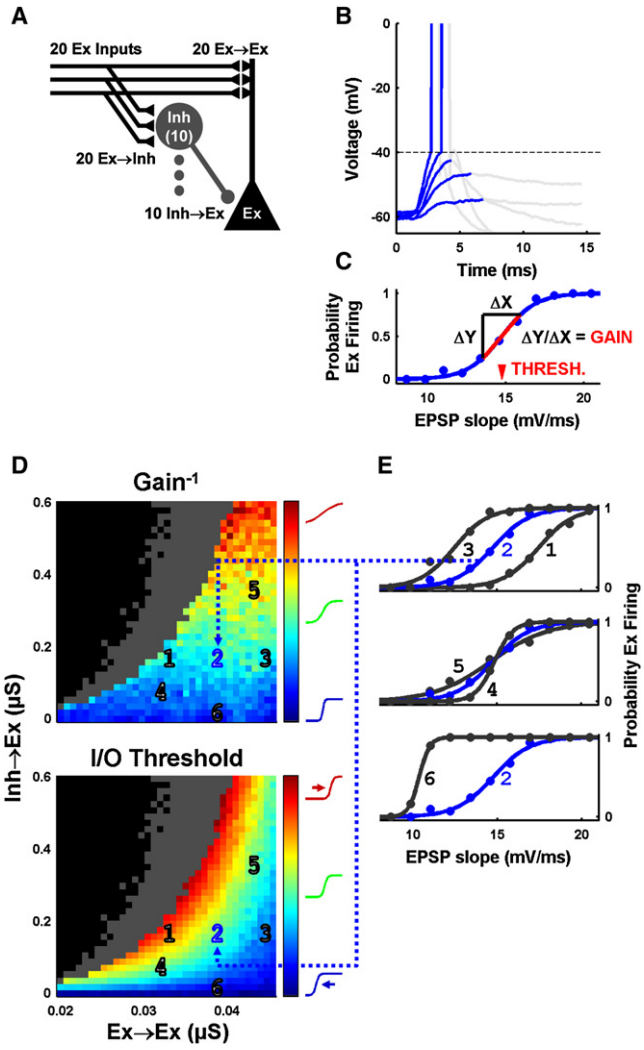

Figure 1. Excitatory and Inhibitory Synaptic Strengths Control the Gain and Threshold of the Neuronal Input-Output Function

(A) Topology of the simulated feed-forward inhibitory circuit.

(B) Sample voltage responses of the Ex unit at different input intensities (see text), for a particular combination of Ex→Ex and Inh→Ex synaptic weights (number 2 in [D]). Voltage traces were colored gray after the peak to ease the visualization of overlapping lines.

(C) I/O function of the Ex unit in (B), obtained by plotting the action potential probability versus the EPSP slope of the voltage traces (in bins, see text and Experimental Procedures).

(D) Parameter scan of the excitatory and inhibitory synapse space. At each coordinate an I/O function was determined for the corresponding Ex→Ex and Inh→Ex synaptic weights. The numbers in the foreground depict the individual I/O functions plotted in (E). Top: the gain (inverse) of each I/O function is plotted in color (range: [0.09 1.10] ms/mV). Hot colors depict an I/O function with a shallow slope, while cold colors depict an I/O function with a very sharp slope. Black depicts coordinates in which the inhibitory synapses were so strong that the Ex unit never fired. In gray the Ex unit fired occasionally, but not yielding enough points to be fitted with a sigmoid. Bottom: as above, but plotting the threshold of the same I/O curves (range: [10 20] mV/ms). Hot colors depict I/O functions with high threshold while cold colors depict I/O functions with low threshold. The dashed arrow highlights that a single I/O function is defined by two properties (gain and threshold).

(E) Sample individual I/O functions. The gain *and* threshold of these sigmoids are highlighted in the corresponding plots in (D) by the corresponding numbers.

Additionally, to date no general framework exists as to how excitatory and inhibitory synaptic plasticity interact to control the I/O function of a neuron.

To understand how synaptic plasticity alters the behavior of neurons it is necessary to characterize the I/O function in response to *synaptically* evoked activity. It is important to note that the issue of long-term changes in I/O functions produced by synaptic plasticity is distinct from the rapid "online" changes in gain of the firing rate curve—such as the modulation produced by the position of the eyes (Trotter and Celebrini, 1999) or attention (McAdams and Reid, 2005)—that are critical for many sensory and motor computations (Salinas and Thier, 2000). It has been shown that the gain modulation of the firing rate curves is dependent on background synaptic activity (Chance et al., 2002; Murphy and Miller, 2003; Prescott and De Koninck, 2003; Cardin et al., 2008). These studies typically examine steady-state firing rate in response to injected depolarizing current steps and address how firing rate is modulated on a rapid time scale for online computations. The distinct question addressed here pertains to the probability a neuron will spike in response to a brief stimulus depending on the *strength* of the active excitatory and inhibitory synapses. The focus on the early response to stimuli is important, particularly in sensory systems, because it is the transient response that is critical to many sensory computations (Durstewitz and Deco, 2008; Rabinovich et al., 2008), and brief sensory stimuli often elicit only one or a few spikes (DeWeese et al., 2003; Wang et al., 2005). Indeed, in many cases steady-state responses are unlikely to contribute to computations (Rolls and Tovee, 1994; Thorpe et al., 1996; Hung et al., 2005; Rabinovich et al., 2008).

While it is established that both EPSPs (Bliss and Lomo, 1973; Dudek and Bear, 1992) and IPSPs (Komatsu, 1994; McLean et al., 1996; Lu et al., 2000; Gaiarsa et al., 2002; Chevaleyre and Castillo, 2003) undergo LTP and LTD, the tradeoff between different types of synaptic plasticity and the computation being performed is not understood. For example, from a computational perspective, what is the functional difference between potentiating excitatory inputs and depressing inhibitory ones? What is the computational benefit of potentiating both EPSPs and IPSPs onto the same postsynaptic neuron (Kairiss et al., 1987; Komatsu, 1994; Xie et al., 1995; Shew et al., 2000; Lamsa et al., 2005; Froemke et al., 2007), which superficially seems self-defeating?

To address these questions, we first developed a computational model which shows that the threshold and gain of neuronal I/O functions can be independently controlled by changes in excitatory and/or inhibitory synaptic strength. We next examined experimentally the prediction of the model by determining the I/O function of neurons in response to manipulation of excitatory and inhibitory synaptic strengths. Our findings indicate that excitatory plasticity in isolation alters the threshold of a neuron's I/O function while keeping the gain constant. On the other hand, balanced changes in synaptic excitation and inhibition can adjust the gain of the neuron's I/O function while maintaining

a constant threshold. This study establishes a framework for understanding the potential function and tradeoff between invoking excitatory and inhibitory plasticity in isolation or in parallel and proposes that I/O function plasticity could be used to optimize the encoding of information.

RESULTS

Theoretical Analysis of the Effects of Excitatory and Inhibitory Plasticity on Neuronal I/O Functions

To examine the effects of changing excitatory and inhibitory synaptic strengths on the neuronal I/O function, we simulated a feed-forward disynaptic circuit (Figure 1A) and examined the response of a single postsynaptic excitatory neuron (Ex) to increasing input intensity, which we represented as an increase in the number of active excitatory and inhibitory synapses (Figure 1B; see Experimental Procedures). In accordance with real neurons, the likelihood of eliciting an action potential is probabilistic as a result of an incorporated "noise" current—representing background synaptic activity and other stochastic processes. The estimation of the spike probability across increasing intensities was fit with a sigmoid function and, as observed experimentally, high intensities led not only to an increased probability of firing but also to a decrease in the spike latency (Pennartz and Kitai, 1991; Figures 1B and 1C).

To understand how different excitatory and inhibitory synaptic weights, corresponding to LTD or LTP of EPSPs and/or IPSPs, modify the I/O function of a neuron, we parametrically varied the strength of Ex→Ex and Inh→Ex synapses. For each pair of synaptic weights we plotted the threshold and gain of the corresponding I/O function, hence describing the behavior of the neuron across synapse space (Figure 1D). These results show that, for fixed levels of inhibitory synaptic strength, modifying the strength of a neuron's excitatory synapses shifts the threshold to the left or right, but has little effect on the gain of the I/O function (Figure 1E, top). A left shift in the threshold indicates that some of the previously subthreshold EPSPs are now suprathreshold. This is because, as excitatory synapses get stronger, it is possible to elicit the same size EPSP at lower intensities, thus recruiting less inhibition (Marder and Buonomano, 2004). This scenario is equivalent to LTP of the Ex→Ex synapses in the absence of other forms of plasticity. In contrast, inhibitory plasticity alone altered both the threshold and gain of the I/O function (Figure 1E, bottom). Interestingly, regulating the excitatory *and* inhibitory synaptic weights in a *balanced* manner allowed neurons to change the gain of their I/O function while maintaining the same threshold, essentially establishing an "iso-threshold" band along the diagonal of the excitatory and inhibitory synapse space (Figure 1E, middle). In contrast to the previously observed shifts in I/O threshold, the change in the gain as a function of excitatory and inhibitory *synaptic strength* has not been previously described experimentally or theoretically.

These theoretical results suggest that one reason excitatory and inhibitory synapses are plastic is to allow for the *independent control* of the gain and threshold of neuronal I/O functions. That is, if the gain has to be changed while maintaining the I/O threshold, parallel excitatory and inhibitory plasticity should be engaged, whereas if the threshold should be changed while maintaining the gain, only excitatory plasticity should be induced.

Synaptic Inhibition Alters the Threshold and Gain of I/O Functions in CA1 Pyramidal Neurons

To test the above predictions, we performed experiments in which we analyzed the I/O function of CA1 pyramidal neurons in hippocampal slices in response to manipulations of the strength of the excitatory or inhibitory synapses. Like most neurons, CA1 pyramidal cells receive robust feed-forward excitation and inhibition; however, in contrast to the majority of cortical areas, the CA1 subfield has little recurrent connectivity, thus providing a reasonable approximation to the simulated disynaptic circuit used above. Effective synaptic strength was manipulated using pharmacology, hyperpolarization, and directly through the induction of single-cell LTP. Given the difficulty in inducing plasticity exclusively at Inh→Ex synapses, uncertainties regarding the protocols that induce inhibitory plasticity, and the variability of results (Xie et al., 1995; Lu et al., 2000; Shew et al., 2000; Gaiarsa et al., 2002; Chevaleyre and Castillo, 2003), we limited our manipulations of inhibitory strength to pharmacological means to alter Inh→Ex transmission independently of the Ex→Ex and Ex→Inh strengths.

While recording in whole-cell configuration, we first examined the effects of low concentrations (2–3 μM) of the $GABA_A$ antagonist bicuculline on the neuronal I/O function. As already reported (Abraham et al., 1987; Marder and Buonomano, 2003), there was a robust leftward shift of the threshold (Figures 2B and 2C, dark blue versus red, 9.9 ± 1.1 versus 4.6 ± 0.6 mV/ms, $p < 0.001$). Here we show that in agreement with the above simulations (Figure 1E, bottom), there was also an increase in the gain of the I/O function (0.40 ± 0.06 versus 0.94 ± 0.08 ms/mV, $p < 0.001$). Upon washout of the drug, the threshold and gain of the I/O function returned to baseline (Figures 2B and 2C, light blue, gain: 0.42 ± 0.05 ms/mV, threshold: 10.0 ± 1.0 mV/ms). The same results were also observed using 10–15 μM picrotoxin (baseline threshold: 8.4 ± 0.43mV/ms, gain: 0.60 ± 0.14 ms/mV; PTX threshold: 2.0 ± 0.30, gain: 1.30 ± 0.23; n = 3; data not shown).

Experimental Dissociation of Shifts in Threshold and Changes in Gain

In the above experiments, it could be argued that an increase in gain is inextricably linked to the leftward shift in I/O threshold. To establish that it is possible to dissociate changes in threshold and gain, we tonically hyperpolarized the cells (mean: 9.7 ± 2.2 mV; range: 5–13 mV) after collecting the baseline and bicuculline I/O curves (Figures 3A and 3B). Tonic hyperpolarization will alter all synaptic driving forces, however, under reduced inhibition (due to bicuculline) its primary functional effect is a decrease in excitation (i.e., even though EPSP amplitude may be larger, a neuron that was firing will cease to do so because the peak EPSP is farther from action potential threshold). Thus, hyperpolarization together with the necessary increase in stimulation intensity to make the neuron fire shifts the I/O curve rightwards, toward values closer to baseline but, interestingly, does not affect the gain (Figures 3A and 3B, red versus orange,

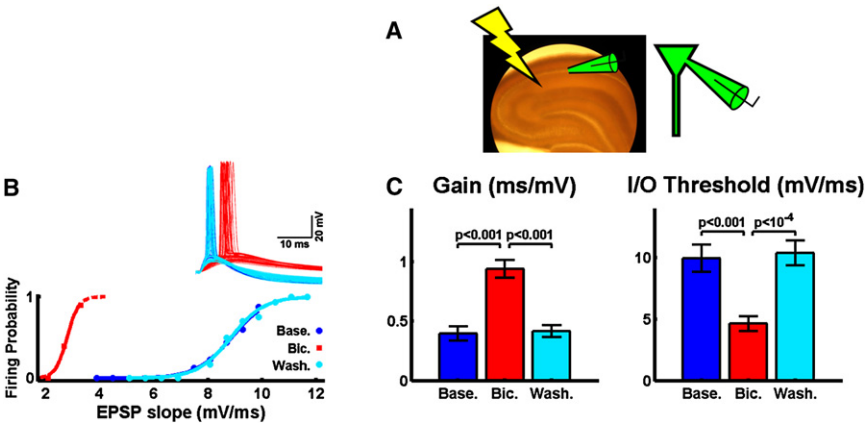

Figure 2. Decrease in Inhibitory Strength Decreases the Threshold but Increases the Gain of Neuronal I/O Functions

(A) Schematic placement of the stimulating and whole-cell recording electrodes.

(B) Example of a bicuculline experiment. Dark blue: I/O function of an intracelullarly recorded CA1 pyramidal neuron, in standard ACSF. Red: I/O function of the same neuron in the presence of 3 μM bicuculline. Light blue: I/O function after 10 min washout of bicuculline. Inset: Sample voltage traces for each of the conditions.

(C) Average gain and threshold for the manipulations described in (B) (n = 8).

gain: 0.96 ± 0.09 versus 0.90 ± 0.08 ms/mV, $p > 0.50$, threshold: 4.4 ± 0.4 versus 7.2 ± 0.5 mV/ms, $p < 10^{-5}$). These results show that changes in threshold and gain can be dissociated and, indirectly, support the proposal that parallel changes in excitation and inhibition may serve to maintain a constant threshold while modifying the gain of the I/O function of a neuron (Figure 1E, middle).

LTP Alters the Threshold While Maintaining the Gain of I/O Functions

Early studies on LTP established that it produces a leftward shift of the I/O curve (Bliss and Lomo, 1973; Andersen et al., 1980; Bliss et al., 1983). The mechanisms underlying the leftward shift remain incompletely understood, in part because some of the induction protocols used (e.g., presynaptic high frequency stimulation) may induce plasticity at other synapses (Ex → Inh and/or Inh → Ex) (Kairiss et al., 1987; Komatsu, 1994; Xie et al., 1995; Shew et al., 2000) as well as changes in intrinsic excitability or dendritic integration (Chavez-Noriega et al., 1990; Daoudal and Debanne, 2003; Xu et al., 2005; Campanac and Debanne, 2008). Nevertheless, it has been shown that single-cell associative pairing protocols can also induce left shifts in the I/O function (Marder and Buonomano, 2004), which is consistent with our theoretical framework. However, the effect of LTP of excitatory synapses on the gain of the neuronal I/O function has not been addressed.

To examine this issue we performed intracellular experiments with high resistance micropipettes (70–90 MΩ) to prevent washout of LTP (Lamsa et al., 2005). LTP was induced in single neurons with a pairing protocol that has previously been shown not to induce changes in inhibition or intrinsic excitability (Barrionuevo and Brown, 1983; Gustafsson et al., 1987; Marder and Buonomano, 2004). Specifically, pairing intracellular depolarization (100 ms) with a train of four presynaptic stimuli (40 Hz; 60 pairings at 0.2 Hz) resulted in a 79% ± 17% increase in the EPSP slope (we only included experiments with LTP > 10% in this analysis). The induction of LTP caused a left shift (7.4 ± 0.5 versus 5.6 ± 0.8 mV/ms, $p < 0.05$) and, in agreement with the theoretical predictions, did not induce any change in the gain (0.59 ± 0.07 versus 0.57 ± 0.07 ms/mV, $p > 0.80$) of the neuronal I/O function (Figures 4B and 4C).

As mentioned above, the mechanisms underlying the left shift in the I/O function (E-S potentiation) remain controversial and other groups have suggested that it could be due to changes in intrinsic excitability (Sourdet et al., 2003; Frick et al., 2004; Losonczy et al., 2008). A further complicating set of issues is that intracellular techniques can alter the neuronal I/O function as a result of washout (Kato et al., 1993; Staff and Spruston,

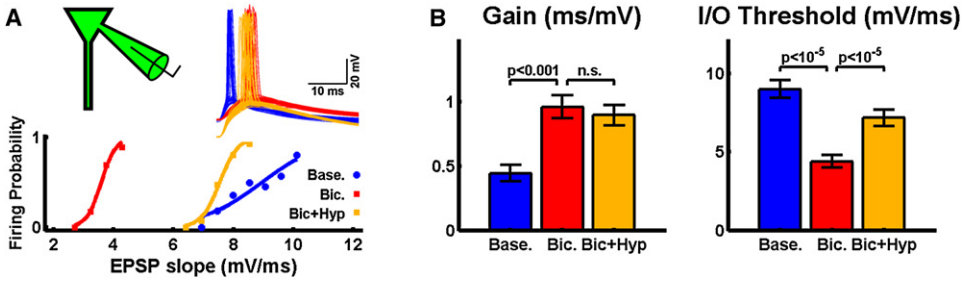

Figure 3. Dissociation of Changes in Gain and Threshold

(A) Bicuculline followed by hyperpolarization experiment. Dark blue: I/O function of an intracelullarly recorded CA1 pyramidal neuron, in whole-cell mode in standard ACSF. Red: I/O function of the same neuron in the presence of 3 μM bicuculline. Orange: I/O function of the same neuron in the presence of bicuculline and hyperpolarized by 12 mV. Inset: Sample voltage traces for each of the conditions.

(B) Average gain and threshold for the manipulations described in (A) (n = 12). Notice that the hyperpolarization, associated with the increase in stimulation intensity necessary to make the neuron fire, increases the I/O threshold in a statistically significant manner, without inducing significant changes in the gain.

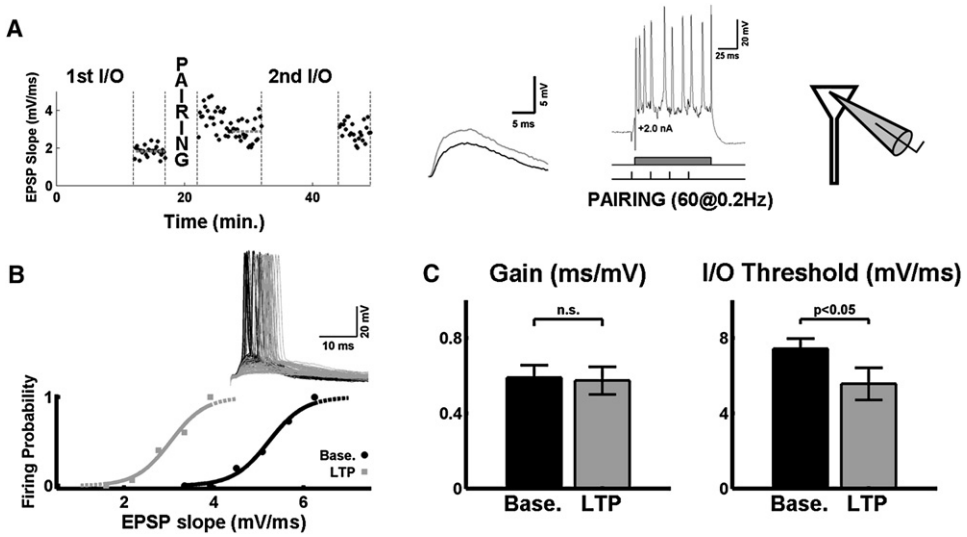

Figure 4. Potentiation of the Excitatory Strength Decreases the Threshold without Changing the Gain of Neuronal I/O Functions

(A) EPSP slopes recorded with a sharp microelectrode during the course of an associative LTP experiment. Voltage traces on the middle represent average sample PSPs from 5 min. after the first I/O and 5 min before the second I/O. The voltage trace on the right shows a sample of the pairing depolarization.

(B) I/O functions before and after the associative LTP pairing protocol. The threshold of the I/O function decreases (left shift), but the gain is left unchanged. Inset: sample voltage traces for each of the conditions.

(C) Average gain and threshold of baseline and LTP I/O curves (n = 11). The associative pairing protocol results in a decrease in the threshold and no changes in gain of the neuronal I/O functions.

2003; Lamsa et al., 2005; Xu et al., 2005), changes in cell input resistance, or changes in the balance of excitation and inhibition (Zhang et al., 1991; Staley and Smith, 2001). To avoid any potential methodological artifacts and determine if global changes in intrinsic excitability could have influenced the above results, we performed experiments in tight-seal cell-attached configuration—which does not rupture the cellular membrane—and included a second unpaired control pathway in the LTP experiments. Given that the cell-attached technique does not allow recording subthreshold responses, we estimated the average input to the neuron by recording the field EPSP from an electrode placed in stratum radiatum in a line perpendicular with the cell body layer (Figure 5A; Andersen et al., 1980; Zalutsky and Nicoll, 1990). The high-resistance cell-attached configuration does not rupture the membrane (seal > 1 GΩ), but still allows the injection of positive current through the electrode and the recording of the spikes (Perkins, 2006; Houweling and Brecht, 2008; Figure 5B, middle). By pairing this depolarization (100 ms) with single presynaptic stimuli (60 pairings at 1Hz), we consistently observed leftward shifts in the I/O functions (11/13 experiments) and, in agreement with the previous results, no change in gain (Figures 5C and 5D; threshold: 74% ± 5% $p < 0.001$, gain: 97% ± 12% $p > 0.80$). Importantly, the unpaired control pathway onto the same cell showed no horizontal shift or change in gain (threshold: 108% ± 10% $p > 0.70$; gain: 108% ± 10% $p > 0.70$). There was a significant difference in the threshold between the paired and unpaired pathways ($p < 0.005$), but no difference in the gain ($p > 0.50$, Figure 5D). These results establish that the pairing-LTP induced left shift is not a result of general changes in intrinsic excitability. Additionally, as in the LTP experiments shown in Figure 4, the fact that there was no change in the gain of the I/O function is consistent with the prediction made in Figure 1. However, it should be stressed that the interpretation of I/O function in these cell-attached experiments is constrained by the fact that the extracellular fEPSP was used to construct the I/O function.

Together, these results demonstrate that LTP produces a leftward shift in the absence of a change in gain and that this effect is not likely to be a result of any cell-wide form of intrinsic plasticity. In contrast, a decrease in inhibition is accompanied by a change in gain, in addition to the change in threshold.

Mechanisms of the Changes in Gain and Threshold Induced by Synaptic Plasticity

The simulations and experiments above indicate that increasing excitatory (E-LTP) or decreasing inhibitory synaptic strength (I-LTD) both produce left shifts in the threshold of the I/O function; however, the latter also induces an increase in the gain (the potential computational relevance of these forms of plasticity is addressed in the Discussion). Next, we used the computational model to understand the origin of the change in gain associated with changes in synaptic inhibitory strength. It is important to point out that excitatory and inhibitory synaptic plasticity produce fundamentally different changes in the postsynaptic potential (PSP) waveform: excitatory plasticity changes the slope and peak of the PSP, while changes in inhibition alter the peak and width of the PSP (see Figure S1 available online; Buonomano and Merzenich, 1998; Pouille and Scanziani, 2001). As a consequence of the inherent asymmetry between excitatory and inhibitory plasticity, imposed primarily by the delay of inhibition in relation to excitation, small changes in excitation are proportionally more effective in altering the PSP peak

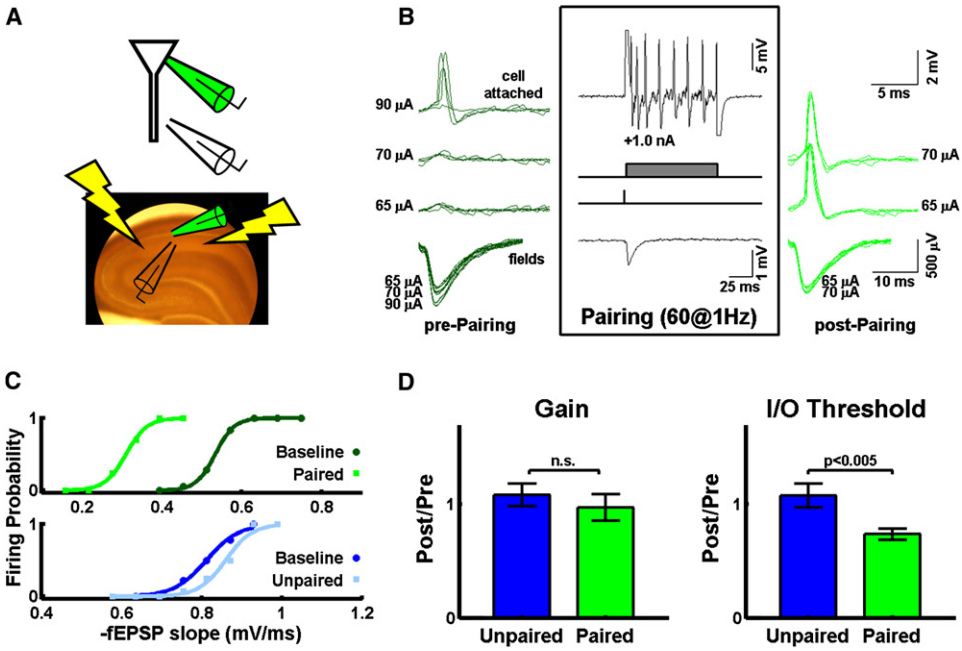

Figure 5. LTP-Induced Threshold Left Shifts with Constant Gain Are Not Due to Global Changes in Excitability

(A) Schematic placement of the stimulating and cell-attached and field recording electrodes.

(B) Example of the potentiation protocol. Left: sample voltage traces recorded from the cell-attached (top) and field (bottom) electrodes at three different intensities. There are four traces per intensity. Middle: associative pairing protocol. Presynaptic stimulation was paired with 100 ms postsynaptic depolarization 60 times at 1 Hz. Right: voltage traces for the same intensities as before (the highest intensity was no longer used to optimize the estimation of the I/O functions). Notice the increased action potential probability.

(C) Sample I/O functions before and after the associative pairing protocol illustrated in (B). Top: paired pathway. The threshold of the I/O function decreases (left shift), but the gain is left unchanged. Bottom: control pathway. The I/O function is unchanged supporting the existence of no global changes in excitability.

(D) Average change in gain and threshold, relative to baseline, for the paired and unpaired pathways (n = 13). The associative pairing protocol results in a decrease in threshold and no changes in gain of the neuronal I/O functions. In contrast, the unpaired pathway shows no changes in either the threshold or gain.

than changes in inhibition (Figure S1). On the other hand, the fact that inhibitory plasticity determines the width of the PSP is an important factor in determining the gain of the I/O function because the wider the PSP the longer it borders action potential threshold—hence, subsequent small increases in the PSP slope will result in sharp increases in spike probability and the I/O gain (Figure S2).

There are a number of interrelated properties that jointly contribute to determining the I/O gain and whether or not it changes after synaptic plasticity. Below we first address the mechanisms responsible for the observed changes in the I/O function in response to inhibitory or excitatory plasticity in isolation. Additionally, the issue of I/O gain control is further discussed in the Supplemental Data.

I-LTD

Consider a "baseline" I/O function (blue curve in Figure 6A), and the stimulation intensity (S_{50}) which elicits the EPSP slope that defines the threshold of this I/O curve (Figure 6D; that is, the EPSP slope that generates action potentials with 50% probability). If one induces I-LTD (Figure 6A, red curve), the EPSP slope at the original S_{50} will remain largely unchanged, since it is mainly determined by the excitatory strength. Yet, the PSP width and height will *increase*; hence, the same EPSP slope will yield action potentials with increased probability. To find the new I/O threshold one must *decrease* the stimulation intensity until it yields an EPSP slope where the neuron fires action potentials again with 50% probability (Figure 6A, left red I/O), thus accounting for the left shift of the threshold of the I/O curve. But why does the gain change? Compared with an I/O of the same threshold, but with the same gain as the baseline curve (dark green trace in Figure 6A, see "E-LTP" below), changes in stimulation intensity will produce a smaller change in the inhibitory conductance (gInh) because inhibitory synapses are weaker after I-LTD (Figure 6C, left red). This can also be visualized in Figure 6D, in which the crosses and squares represent the peak IPSC and EPSC amplitudes as function of stimulation intensity. At stimulation intensities straddling 50% firing probability of the I-LTD I/O curve (red line), the red crosses change at a slower rate than the green crosses for the corresponding S_{50} point (yet there is relatively little change in the red and green EPSC amplitudes, squares, see below). Hence, as intensity increases, the rate of change of excitation is higher than that of inhibition (compared to the E-LTP isothreshold case, green lines), resulting in a faster transition from a low to high probability state (i.e., a higher gain).

E-LTP

Ex→Ex LTP is similar to Inh→Ex LTD in the sense that both make it easier for the cell to fire an action potential at any given

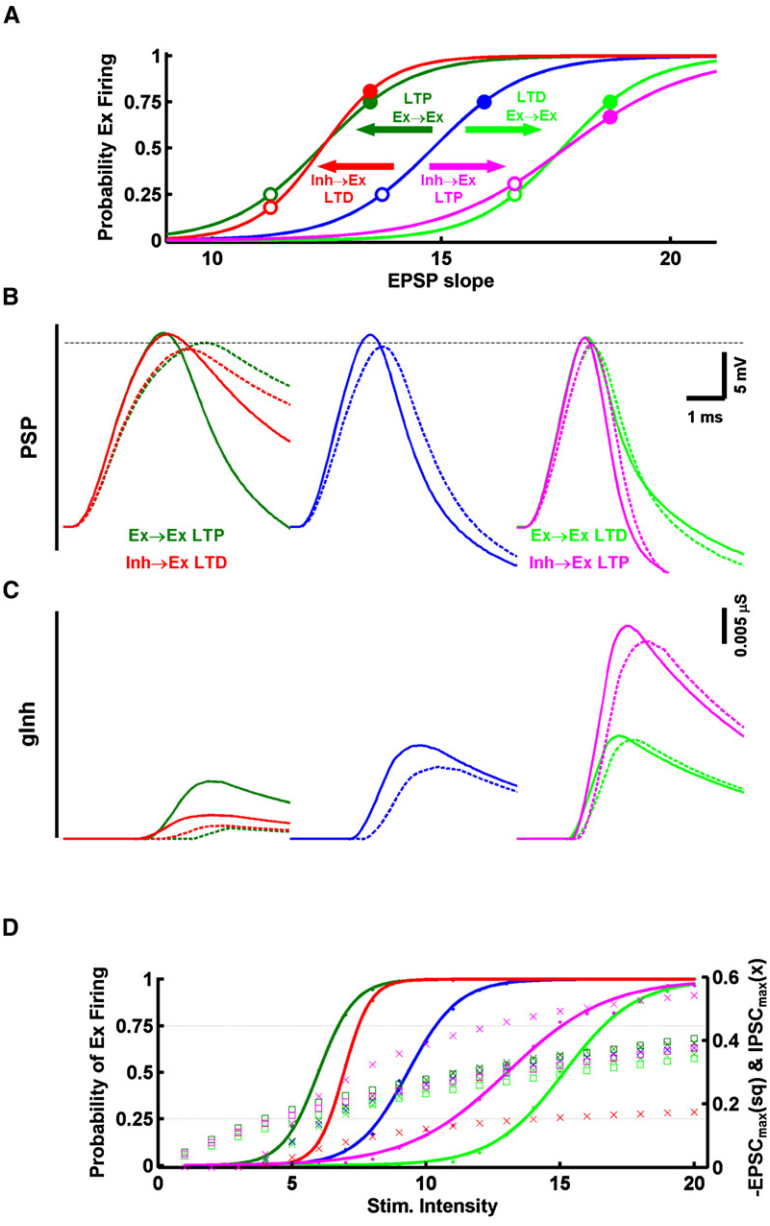

Figure 6. Mechanisms Underlying the Change in I/O Gain Produced by Synaptic Plasticity

(A) Neuronal I/O functions from the model at different values of Ex→Ex and Inh→Ex synaptic strength. Blue curve is the "baseline," the green curves result from Ex→Ex plasticity and the red/magenta curves from Inh→Ex plasticity. Note that LTD of Inh→Ex and LTP of Ex→Ex produced an equal left shift in threshold; however, inhibitory plasticity also resulted in an *increased* gain; conversely, LTP of Inh→Ex and LTD of Ex→Ex produced the same right shift, with a *decreased* gain in the former case. The points with 0.25 and 0.75 probability of firing are highlighted in the blue and green curves. In the red/magenta curves we highlighted the EPSP slope that yielded 0.25 or 0.75 in the corresponding isothreshold *green curve*.

(B) Voltage traces with EPSP slopes highlighted with the circles in (A) (V_m noise and action potentials were removed). Dashed and solid lines represent the PSPs that would yield ~25% and ~75% probability of firing, respectively (see [A]).

(C) Inhibitory conductance traces of the corresponding PSP traces in (B). Notice that at the same EPSP slopes, the inhibitory change from 0.25–0.75 is smaller for Inh→Ex LTD as compared to Ex→Ex LTP, which causes an I/O function with a higher gain. Conversely, the inhibitory change from 0.25–0.75 in Inh→Ex LTP is bigger as compared to Ex→Ex LTD, which results in an I/O function with decreased gain.

(D) Same data as in (A) but plotted as a function of stimulus intensity (solid sigmoid curves). The maximum EPSC (squares) and IPSC (crosses) amplitudes are also plotted, in the color corresponding to each of the I/O functions.

EPSP slope, shifting the I/O curve leftwards (green line, Figure 6A). When one increases the strength of excitatory synapses, the *same* stimulation intensity yields a *bigger* EPSP slope and increased spike probability. Thus, to return to the initial EPSP slope, one has to *decrease* the stimulation intensity, which has the consequence of decreasing the recruitment of inhibitory neurons and increasing their latency. As a result, the original EPSP slope is now accompanied by less inhibition and has increased probability of generating an action potential, which means that the whole I/O curve has shifted to the left.

However, in the case of potentiation of excitatory synapses (or conversely Ex→Ex LTD, light green line, Figure 6A), the left shift is qualitatively different from the left shift caused by decreased inhibitory strength given that the gain of the I/O function stays the same. As in the case of I-LTD, E-LTP produces an effective shift in the range of stimulation intensities straddling the I/O threshold (Figure 6D). An important consequence of this is that, even in the absence of plasticity at the inhibitory synapses, there will be an effective change in the levels of inhibition around the new I/O threshold. As shown in Figure 6D (green crosses), this left shift will result in larger changes in inhibition for a given change in stimulation intensity, in the relevant range of the I/O curve. Specifically, as a result of the nonlinear and asymptotic nature of the IPSC versus stimulation intensity curve, decreasing the relevant stimulation intensities effectively produces an increase in the rate of change in inhibition. Thus, it is possible to maintain the balance between the rate of change of excitation and inhibition even after E-LTP because the IPSC versus stimulation intensity function is now operating in a regime with a higher slope (note the larger change in IPSC amplitudes over the range in which firing probability changes from 25% to 75%, dashed and solid dark green lines, Figure 6C). In other words, the relationship between EPSC and IPSC amplitudes as a function of stimulation intensity is relatively constant for I/Os that underwent excitatory plasticity (as shown in Figure S3 for the I/O functions depicted in Figure 6). Note that although the IPSC and EPSC amplitudes are balanced across intensities, higher intensities will still be more effective at eliciting spikes because the changes in EPSC and IPSC latency favor excitation (see Supplemental Experimental Procedures; Figure S6)—for example, in the extreme a strong

EPSP can generate a spike regardless of inhibitory synaptic strength if voltage crosses spike threshold before the Inh neurons fire.

Thus, an important factor underlying the isogain bands of Figure 1D is the relationship between IPSCs as a function of stimulation intensity (crosses in Figure 6D) and EPSCs as a function of intensity (squares in Figure 6D). More specifically, these functions scale in an approximately linear fashion over most intensities, consequently, at different intensities the IPSC/EPSC balance is approximately constant. Given that excitatory plasticity does not change the IPSC/EPSC ratio significantly (Figure S3), for the reasons that were mentioned earlier (Figure S1), the change in the relevant range of stimulation intensities caused by excitatory plasticity also does not alter the IPSC/EPSC ratio significantly. If, however, the IPSC versus stimulation intensity function is disrupted in a manner that significantly alters the IPSC/EPSC ratios across intensities then excitatory plasticity will alter the gain of the I/O (see Supplemental Experimental Procedures and Figure S4). Thus, the model assumptions regarding the relationship between inhibition and stimulation intensity are crucial. Importantly however, they are supported by experimental findings that demonstrate that synaptic drive increases asymptotically as a function of intensity (Costa et al., 2002; Kushner et al., 2005) and that excitation and inhibition remain balanced across stimulation intensities (Gabernet et al., 2005). Additionally, the fact that our own experimental findings confirm that E-LTP does not change the I/O gain, further supports our model.

It can be seen that since Ex→Ex potentiation shifts the I/O curve leftwards without changing its gain and that Inh→Ex potentiation can shift the I/O rightwards with a decrease in gain (Figure 6A, magenta curve), that the appropriate mix of both forms of plasticity could change the I/O gain without altering the threshold. Thus, simultaneous Ex→Ex and Inh→Ex LTP, as reported by Froemke et al. (2007), may function to maintain the threshold of a neuron while decreasing its gain (Figure 1E, middle; Figure S2).

The above discussion of gain control highlights the subtlety and nonlinear nature of even a relatively simple disynaptic circuit, particularly in relation to the dynamic nature of the balance of excitation and inhibition (Marder and Buonomano, 2004). Indeed, it is important to stress that a limitation of the above analysis is that it is actually not the balance of excitation and inhibition at the peak EPSC and IPSC values that governs whether or not a neuron fires, but at earlier and intensity-dependent points near the peak the PSP (Supplemental Experimental Procedures; Figure S5). Thus, a detailed and quantitative description of the relative contribution of different factors to gain control, including the latency and jitter of the inhibitory neurons, will benefit from future theoretical studies.

DISCUSSION

We have used theoretical and experimental techniques to examine how changes in the strength of excitatory and/or inhibitory synapses alter the response of neurons to transient synaptic stimulation. A large number of studies have described how long-term plasticity of excitatory and/or inhibitory synapses affect subthreshold responses, however, there has been less focus on how these changes alter the input-output characteristics of neurons—which is what ultimately determines the computational and behavioral relevance of synaptic plasticity. The general intuition regarding LTP of Ex→Ex synapses is that it will increase the likelihood of a given input generating a postsynaptic spike. However, as shown in our simulation, if LTP is accompanied by a parallel increase in the strength of Inh→Ex synapses, additional nonlinear behaviors take place. Specifically, the threshold can remain the same, but the likelihood of eliciting a spike can increase at low intensities, but actually decrease at high intensities (i.e., a decrease in gain; Figure 1E, middle; Figure S2).

As mentioned in the Introduction, the current study addresses a distinct question from those that characterized the modulation of the response of neurons by different levels or characteristics of background activity (Ho and Destexhe, 2000; Chance et al., 2002; Murphy and Miller, 2003; Shu et al., 2003; Cardin et al., 2008). Because these previous studies were aimed at addressing "online" changes in gain they did not examine the consequences of synaptic plasticity, nor the changes in firing probability in response to synaptic inputs (but see Prescott and De Koninck, 2003). Additionally, studies using direct current injection to emulate excitatory or inhibitory currents do not capture the inherent temporal interactions between excitatory and inhibitory synapses, which are critical in determining the output of neurons (Pouille and Scanziani, 2001; Wehr and Zador, 2003; Marder and Buonomano, 2004; Wilent and Contreras, 2005). Here, the issue of how synaptic plasticity of excitatory and inhibitory synapses alters spike probability relates to learning and memory and the processing of sensory stimuli. Specifically, in sensory areas, computations often rely on the input-output characteristics of cortical neurons in response to brief sensory stimuli that tend to elicit a single or a few spikes (Kilgard and Merzenich, 1998; Perez-Orive et al., 2002; DeWeese et al., 2003; Tan et al., 2004; Hung et al., 2005; Higley and Contreras, 2006). Changes in I/O threshold as a result of LTP of Ex→Ex synapses have been well documented experimentally (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973; Andersen et al., 1980; Staff and Spruston, 2003) and are due, at least in part, to changes in the relative balance of excitation and inhibition (Marder and Buonomano, 2004), although changes in intrinsic excitability or dendritic integration may also contribute to the shift in I/O threshold (Sourdet et al., 2003; Staff and Spruston, 2003; Frick et al., 2004; Campanac and Debanne, 2008). To the best of our knowledge, this is the first report of synaptic-dependent changes in the gain of the neuronal I/O function, which are primarily linked to inhibitory plasticity.

Excitatory and Inhibitory Plasticity

Postsynaptic potentials elicited by sensory stimuli are almost always composed of an excitatory and inhibitory component (Wehr and Zador, 2003; Tan et al., 2004; Higley and Contreras, 2006). One of the questions posed in the Introduction was what would be the functional and computational difference between increasing the strength of excitatory and decreasing the strength of inhibitory synapses. While the computational role of excitatory plasticity has been embedded within a solid theoretical

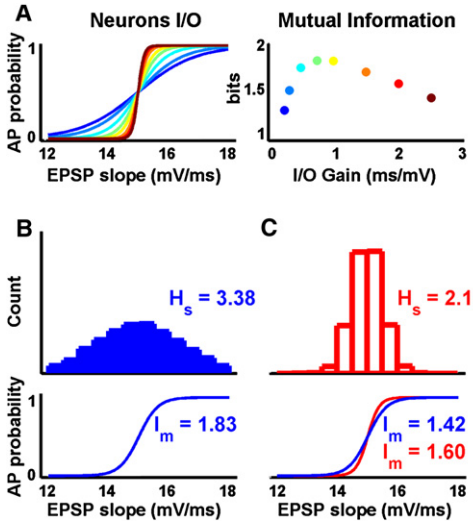

Figure 7. Neurons Can Maximize Information Transmission by Adjusting Their I/O Function

(A) Left: I/O functions with different gains. Right: information that a population of 15 neurons with the same I/Os would be able to convey, as a function of their gain and in response to the Gaussian distributed stimuli depicted in (B).

(B) Plot of the stimulus distribution used in (A), and the I/O function that maximizes mutual information (I_m = 1.83 bits, green curve in [A]). H_s is the entropy of the stimulus, which corresponds to the maximal mutual information.

(C) If the stimulus distribution changes (upper panel), the I/O function depicted in (B) would carry less information (blue sigmoid, 1.42 bits). However, by adjusting the I/O function, the neuron's response can now code for 1.60 bits. Note that the maximal information H_s also varies according to the distribution.

framework since Hebb (Hebb, 1949; von der Malsburg, 1973; Bienenstock et al., 1982; Miller et al., 1989), the computational role of inhibitory synaptic plasticity remains much more speculative. As with excitatory plasticity, inhibitory plasticity is likely to play multiple roles both in maintaining the proper homeostatic balance and preventing runaway excitation (Rutherford et al., 1997; Karmarkar and Buonomano, 2006). It is also likely to play a role in mnemonic plasticity (Kim and Linden, 2007), in masking excitatory responses during experience-dependent plasticity (Zheng and Knudsen, 1999; Foeller et al., 2005) or contribute to the development of cortical maps (Hensch, 2004),

Here, we propose a more detailed computational framework regarding the function of inhibitory plasticity. Specifically, that in contrast to excitatory plasticity, changes in inhibition allow neurons to control the gain of their I/O function. Indeed the fact that evoked activity generally elicits an EPSC followed by an IPSC (a delay produced by the additionally "synaptic step") ensures the inhibitory plasticity is well suited to control the width of the PSP (the integration window—Pouille and Scanziani, 2001; Gabernet et al., 2005) and thus the gain of the neural I/O function. An interesting corollary is that excitatory and inhibitory plasticity in parallel may provide a mechanism by which neurons can alter the I/O gain while maintaining their I/O threshold.

Computational Relevance

The computational advantage of controlling the threshold and gain of neurons has been examined in a number of contexts (Laughlin, 1981; Dean et al., 2005). To illustrate how the ability to alter the threshold and/or gain of an I/O function can optimize the encoding of information, we provide a simple example in Figure 7. We considered a small population of neurons, with the same I/O function, and quantified the information about the intensity of the stimulus (EPSP slope) that is encoded in the response of the population (the total number of spikes). The mutual information (I_m) will depend both on the distribution of the stimulus as well as on the I/O function of the neurons (Figure 7A). For example, for the broad distribution shown in Figure 7B there is an optimal I/O gain that will allow the neurons to encode 1.83 bits. If the stimulus distribution becomes more narrow (decrease in entropy), the previous gain is no longer optimal—however, changing the gain can bring the system back into an optimal range (Figure 7C). Thus, the ability to adjust the gain of the I/O function, while maintaining threshold, would allow neurons to increase their information capacity, which we propose may be achieved by balanced synaptic changes in excitation and inhibition.

Conclusion

Our results indicate that orchestrated regulation of excitatory and inhibitory synaptic strength provides control over both the threshold and gain of I/O functions, which in turn could be used to optimize information processing. If this notion is correct it would imply that a set of learning rules is in place that would endow neurons with two general modes of I/O plasticity. *Threshold plasticity*, consisting primarily of changes in excitation, would leave gain unchanged. *Gain plasticity*, consisting of parallel changes in excitation and inhibition, would allow altering the gain independently of the threshold (Figure 8).

EXPERIMENTAL PROCEDURES

Model

Simulations were performed with NEURON (Hines and Carnevale, 1997). Each neuron was simulated as an integrate-and-fire unit. The excitatory unit (Ex) had

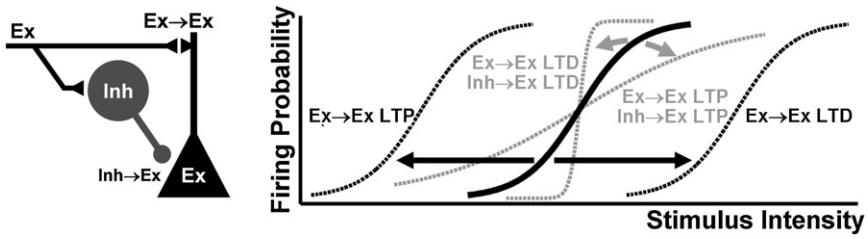

Figure 8. I/O Threshold and Gain Plasticity

In disynaptic circuits, plasticity of the excitatory synapses onto a neuron leads to horizontal shifts of the I/O function without changing the gain (*threshold plasticity*, dashed black sigmoids). Balanced changes in excitation and inhibition change the gain of the I/O function without changing the threshold (*gain plasticity*, gray sigmoids). Different combinations of excitatory and inhibitory plasticity can produce arbitrary plasticity of threshold and gain.

two compartments, representing the soma and an apical dendrite; inhibitory units (Inh) had a single compartment. The total synaptic weight onto each Inh neuron was distributed so that increases in intensity corresponded to increases in the number of Inh neurons recruitedand progressively decreased their latency (Marder and Buonomano, 2004). I/O curves were determined in the same manner as for experimental intracellular recordings, by measuring the EPSP slope and spike probability at all intensities, the gain and threshold were determined as described bellow. Further details and parameters are presented in the Supplemental Data online. We also performed the simulations shown in this paper using a Hodgkin-Huxley implementation of the Ex unit and the results were qualitatively similar (data not shown).

Mutual Information

The information transmission simulations were performed in MATLAB. Briefly, stimuli were withdrawn from a normal distribution with variance 2 or 0.25 and activated a population of 15 neurons, each with the same I/O function represented in the figure. Whether or not a neuron spikes in response to a given EPSP was determined directly from the I/O function. The mutual information is given by $I_m = H_s + H_r - H_{sr}$ where $H_i = -\sum P_i \log_2(P_i)$. The response r corresponds to the number of active neurons and sr is the joint probability of the stimulus and the response.

Electrophysiology

Slice Preparation

Experiments were performed at a temperature of 31°C ± 1°C on acute 400 μm transverse hippocampal slices from 17- to 28-day-old Sprague-Dawley rats in standard ACSF (see Supplemental Data).

Recordings

Electrodes were positioned in area CA1. Whole-cell recordings were considered acceptable if they met the following criteria: resting potential below −55 mV, input resistance larger than 80 MΩ, and overshooting action potentials. Sharp recordings were considered acceptable if they met the following criteria: resting potential below −55 mV, input resistance of 30 MΩ, and overshooting action potentials. In tight-seal cell-attached recordings, if the seal dropped to <1 GΩ the experiment was aborted. Most commonly, seal values were ~5 GΩ. A second microelectrode was placed extracellularly, in stratum radiatum positioned along a line perpendicular to the cell body layer, to record fEPSPs.

Electrical Stimulation

Electrodes were positioned in the stratum radiatum close to the CA3-CA1 border. In experiments with a control pathway, the second electrode was placed in the stratum radiatum toward the subiculum; the test and control pathway were chosen randomly. The distance between the recording and stimulating sites was between 150 and 450 μm. Biphasic, constant current, 100 μs stimuli were delivered at 10–15 s intervals (if applicable, out of phase and alternately to each pathway). Stimulation intensities ranged from 30–300 μA.

I/O Curves

A series of 60–90 pulses were given at different stimulation intensities, covering a range of responses from subthreshold to supramaximal. I/O curves were constructed by binning the totality of the EPSP (fEPSP) slopes and plotting the center of the bin versus the percentage of successful action potentials in that bin, for the corresponding experimental condition. The data points were fit with a sigmoid: $S = 1/(1 + \exp[(E_{50} - E)/k])$, where E_{50} is the EPSP (fEPSP) slope that yields action potentials 50% of the times (the I/O threshold). The gain was determined by calculating the slope of the linear portion of the sigmoid (between 0.25 and 0.75).

Pairing Protocol

After completion of the baseline I/O curve, single pulse or four pulse (40 Hz) extracellular stimulation was paired with cellular depolarization by injecting positive current through the recording electrode for 100 ms, so that 6–10 action potentials were elicited. The delay between the extracellular stimulation and the onset of the depolarization was 2 ms. The pairing was repeated 60 times at 1 or 0.2 Hz. The second I/O function was determined 10 min. after the pairing protocol.

Statistics

For statistical comparisons of I/O curves, we analyzed the change in threshold and gain. For intracellular experiments, paired t tests were performed. The absolute fEPSP values depend on several factors, including distance of the stimulating electrode and placement of the field electrode. For this reason, the data were normalized to baseline in the extracellular experiments, and t tests were performed to assess if the ratio was significantly different from 1; paired t tests were performed to compare the control and experimental groups. All values are expressed as mean ± SEM.

The composition of the solutions used and further experimental details are presented in the Supplemental Data online.

SUPPLEMENTAL DATA

The Supplemental Data include six figures and Supplemental Experimental Procedures and can be found with this article online at http://www.neuron.org/supplemental/S0896-6273(09)00080-4.

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