

- 27 Guidetti, P. *et al.* (2001) Early degenerative changes in transgenic mice expressing mutant huntingtin involve dendritic abnormalities but no impairment of mitochondrial energy production. *Exp. Neurol.* 169, 340–350
- 28 Hansson, O. *et al.* (1999) Transgenic mice expressing a Huntington's disease mutation are resistant to quinolinic acid-induced striatal excitotoxicity. *Proc. Natl. Acad. Sci. U. S. A.* 96, 8727–8732
- 29 Wong, P.C. *et al.* (2002) Genetically engineered mouse models of neurodegenerative diseases. *Nat. Neurosci.* 5, 633–639
- 30 Rubinsztein, D.C. (2002) Lessons from animal models of Huntington's disease. *Trends Genet.* 18, 202–209
- 31 Kisselev, A.F. and Goldberg, A.L. (2001) Proteasome inhibitors: from research tools to drug candidates. *Chem. Biol.* 8, 739–758
- 32 Lindsten, K. *et al.* (2002) Mutant ubiquitin found in neurodegenerative disorders is a ubiquitin fusion degradation substrate that blocks proteasomal degradation. *J. Cell Biol.* 157, 417–427
- 33 Johnson, E.S. *et al.* (1995) A proteolytic pathway that recognizes ubiquitin as a degradation signal. *J. Biol. Chem.* 270, 17442–17456
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# Cooperative LTP can map memory sequences on dendritic branches

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**Hebbian synaptic learning requires co-activation of presynaptic and postsynaptic neurons. However, under some conditions, information regarding the postsynaptic action potential, carried by backpropagating action potentials, can be strongly degraded before it reaches the distal dendritic synapse. Can these synapses still exhibit Hebbian long-term potentiation (LTP)? Recent results show that LTP can indeed occur at synapses on distal dendrites of hippocampal CA1 neurons, even in the absence of a postsynaptic somatic spike. Instead, local dendritic spikes contribute to the depolarization required to induce LTP. Here, a dendritically constrained synaptic learning rule is proposed, which suggests that nearby synapses can encode temporally contiguous events.**

Synaptic plasticity is believed to be the key mechanism for learning. Hebb [1] proposed the following synaptic learning rule: 'When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficacy, as one of the cells firing B, is increased.' This learning rule has been popularly reinterpreted as 'neurons that fire together wire together'.

Bliss and Lomo [2] showed that large-amplitude, high-frequency electrical stimulation of hippocampal afferents results in long-term potentiation (LTP) of hippocampal synapses. Subsequent work showed that weaker stimuli could also induce LTP if several afferent fibers are stimulated simultaneously. These weak excitatory postsynaptic potentials (EPSPs) can summate, or 'cooperate' [3], to induce sufficient depolarization to induce large  $\text{Ca}^{2+}$  influx and LTP.

What are the mechanisms underlying cooperation in LTP induction? A possible mechanism was uncovered with the discovery that while the action potential is initiated at the axon hillock and propagates forward along an axon, a

backpropagating action potential (BAP) simultaneously propagates into the dendrites [4,5]. When the BAP coincides with an EPSP, they summate non-linearly to generate a large  $\text{Ca}^{2+}$  influx and hence LTP [6]. Thus, if only one synapse or very few weak synapses are activated, cooperation between an EPSP and a BAP results in LTP that is crucially dependent on the relative timing of the EPSP and BAP [7–9].

In cortical and hippocampal pyramidal neurons, however, the BAP amplitude decreases dramatically as a function of distance away from the soma along the dendrites, especially during repeated stimulation [5,10–13], as is typical of LTP induction protocols. Thus, BAPs can be very small by the time they reach the vast number of synapses on the distal dendrites. Can these distal synapses still exhibit Hebbian LTP?

## Synaptic cooperation: plasticity without a postsynaptic spike

Golding *et al.* [14] recently addressed this question. They found that, although there was no LTP induction with weak activation of distal synapses on CA1 neurons (somatic EPSPs of 0.5–1.0 mV), LTP indeed occurred following simultaneous activation of more afferents to produce larger EPSPs ( $>2$  mV at the soma). The magnitude of LTP under these conditions was unaltered when action potential initiation was blocked by hyperpolarization of the soma, or when BAPs were blocked by application of tetrodotoxin (TTX) on the soma. Thus, neither postsynaptic action potential firing nor a somatic depolarization was required for LTP induction on distal dendrites.

Golding *et al.* hypothesized that locally generated dendritic spikes could provide sufficient depolarization, a  $\text{Ca}^{2+}$  transient [15,16] and, hence, LTP. Consistent with this, they found a dendritic-spike-mediated large  $\text{Ca}^{2+}$  influx in the distal dendrites. Conversely, somatic spikes resulted in small, if any,  $\text{Ca}^{2+}$  influx in the distal dendrites.

The amplitude of dendritic spikes during stimulation was a good predictor of the magnitude of subsequent LTP. Further, the distal dendritic LTP was abolished by

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combined application of antagonists of NMDA receptors and of voltage-gated  $\text{Ca}^{2+}$  channels, suggesting that the size of dendritic-spike-mediated  $\text{Ca}^{2+}$  transients in the distal dendrites was a decisive factor in LTP induction. These results convincingly demonstrate that cooperation between EPSPs is sufficient to generate a dendritic spike and LTP *in vitro*. This mechanism opens up several interesting directions, some of which are discussed here.

One question is whether there are conditions when BAPs could induce LTP on distal dendrites. Recent results show that the size of  $\text{Ca}^{2+}$  transients is virtually identical all along the oblique dendrites [17]. If the determining factor in LTP induction is the local  $\text{Ca}^{2+}$  concentration near the NMDA receptors, LTP could be equally likely at the proximal and distal oblique dendrites. However, if the total  $\text{Ca}^{2+}$  influx were the determining factor, this would not be the case. Further, recent experiments show that when EPSPs collide with a BAP, the BAP amplitude is boosted [9,18,19]. It is possible that the spontaneous activity of afferent synapses *in vivo* could provide a sufficient number of EPSPs to boost the BAP so that they travel much farther along the distal dendrites.

Future research regarding cellular properties, such as channel density along the dendrites and the structure of dendritic branching, as well as the pattern of afferent activity *in vivo*, would shed further light on when cooperation between EPSPs and BAPs is a viable mechanism for LTP induction.

### Constraints on synaptic cooperation

Although BAP-based cooperativity could increase the probability of cooperation across large dendritic distances, dendritic-spike-based cooperativity is likely to be more limited spatially, for several reasons. (i) The cable properties of dendrites: most EPSPs *in vivo* are relatively small and several EPSPs have to cooperate to generate a dendritic spike. These small-amplitude EPSPs travel passively and hence their amplitude diminishes significantly with distance and time. (ii) The limited spread of dendritic spikes: dendritic spikes propagate through the dendritic tree even less reliably than BAPs [20]. (iii) Inhibition: inhibition is blocked in typical *in vitro* experiments but inhibitory neurons are active at a high rate *in vivo*, often at a firing rate ten times that of average pyramidal neurons in the hippocampus. Such powerful inhibition can eliminate an EPSP or even a dendritic spike or BAP [21].

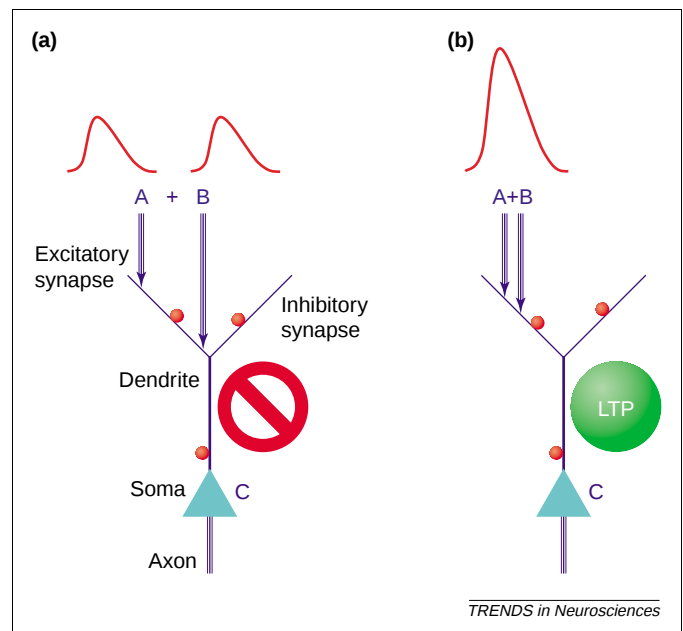
The effects of these constraints on LTP induction *in vivo* are as follows. Consider two excitatory synaptic inputs such that the sum of their EPSPs, but not the individual EPSPs, is sufficient to generate a dendritic spike. Consider first a case in which the two synapses are located far from each other on a dendrite and are coactivated (Figure 1a). The EPSPs would propagate passively along the dendrite, resulting in a decrease in their amplitude. Hence, when the two EPSPs coalesce, the summed EPSP will have smaller amplitude than the sum of the two EPSPs at the sites of their initiation, thereby reducing the probability that this summed EPSP will reach the dendritic spike initiation threshold. Further, during the period when the two EPSPs are passively propagating, activation of any inhibitory synapse located between the two excitatory

synapses would diminish either or both EPSPs, thereby preventing dendritic spike initiation. Thus, both of these mechanisms could significantly reduce the probability of the two EPSPs summing to generate a dendritic spike and, hence, LTP. However, if these two synapses are located near each other (Figure 1b) their EPSPs could coalesce to generate a combined EPSP before they are diminished by passive propagation; thus, lower-amplitude EPSPs than in the previous case would be able to generate a dendritic spike. Further, these EPSPs would be unaffected by activation of inhibitory synapses and hence the two EPSPs would have a larger likelihood of generating a dendritic spike.

Thus, the probability that EPSPs could cooperate to generate LTP would decrease as a function of the distance along the dendrites between synapses. In general, far more than two synapses would have to be coactivated to generate a dendritic spike, which would limit the EPSP cooperation to even smaller regions. Inhibition would also restrict cooperation between BAP and EPSP in a similar fashion.

### Emergent properties of cooperative plasticity

A synaptic learning rule that takes into account these considerations is suggested in Box 1. Such a temporally and anatomically constrained learning rule would have several important and novel emergent properties. In particular, temporally contiguous events would be more likely to be encoded by anatomically contiguous synapses. If the synapses corresponding to temporally contiguous



**Figure 1.** Cooperative long-term potentiation (LTP) can map similar memories on nearby locations on the dendrite. (a) Glutamatergic synapses (blue arrows) from two inputs (i.e. groups of neurons) A and B are located on different dendritic branches of neuron C. Red dots represent inhibitory synapses. Excitatory post-synaptic potentials (EPSPs) resulting from coactivation of A and B would be decremented or even be eliminated by an inhibitory synapse located between the two neurons before they could coalesce to generate a large dendritic spike or LTP. (b) The two excitatory synapses are near each other, so their EPSPs could summate without being affected by dissipation or inhibition, to trigger a dendritic spike and induce LTP. Thus, the information about coactivation of events represented by A and B would be more likely to be encoded by nearby synapses (b) than dispersed synapses (a).

### Box 1. Consequences of cooperative LTP

#### An anatomically constrained synaptic learning rule

Synapses from neurons A and B onto a postsynaptic neuron C will be potentiated if neurons A and B are repeatedly coactivated and if their synapses are located near each other on a dendrite of neuron C.

#### Questions for future research

- (i) Backpropagating action potentials (BAPs) would have a larger probability of reaching proximal dendrites than distal dendrites. Are the learning rules different for proximal versus distal dendrites?
- (ii) Cooperation between an excitatory postsynaptic potential (EPSP) and a BAP results in somatic spike-timing-dependent plasticity [7–9]. Similarly, is there dendritic spike-timing-dependent plasticity?
- (iii) What is the relationship between the direction-selectivity of a neuron and the organization of the afferent synapses on the dendrite [24,26,29,30]?

events are located far from each other, the two EPSPs would have a low probability of cooperating to generate a dendritic spike, and hence potentiate, owing to the mechanisms discussed. Thus, whereas information about individual events could be encoded by a synapse, the organization of the synapses (i.e. dendritic location) would contain information about temporal relationships between events (Figure 1a,b).

Recent work has shown that a temporally asymmetric Hebbian learning could result in encoding of a temporal sequence in terms of the strengths of synapses on a single postsynaptic neuron, such that events occurring earlier in a sequence are encoded by weaker synapses and later events are represented by stronger synapses [22–24]. In other words, Hebbian learning would result in the synaptic strengths corresponding to a temporal sequence to become a monotonic function of the temporal order experience. Consistently, asymmetric excitation, indicative of monotonic synaptic strengths in a temporal sequence, has been found in the direction-selective neurons of various brain regions, such as the rodent hippocampus [24,25] and auditory cortex [26], *Xenopus* optic tectum [27], and cat striate cortex [28].

These results can now be combined with the observations that nearby synapses on a dendrite would encode temporally contiguous events owing to cable properties, dissipation and inhibition. This predicts that the anatomically constrained Hebbian learning rule would result in the temporal order of experience, and hence synaptic strengths within a temporal sequence, to become a monotonic function of distance along the dendrites. Thus, for example, nearby spatial locations would be encoded by anatomically contiguous synapses on a dendritic branch of a hippocampal neuron. In general, nearby locations of a 'stimulus' would be encoded by nearby synapses on a dendritic branch of a direction-selective neuron. Thus, dendritic-spike-mediated learning can map the temporal order of events onto locations on the dendrite. Such a mapping has several advantages, such as fast associative recall of an entire sequence with a limited input. Dendritic-spike-mediated cooperative synaptic plasticity could be a novel and crucial function of the complex dendritic morphology in learning and memory.

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### References

- 1 Hebb, D.O. (1949) *The Organization of Behavior*, Wiley
- 2 Bliss, T.V. and Lomo, T. (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol.* 232, 331–356
- 3 Bliss, T.V. and Collingridge, G.L. (1993) A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361, 31–39
- 4 Stuart, G.J. and Sakmann, B. (1994) Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. *Nature* 367, 69–72
- 5 Spruston, N. *et al.* (1995) Activity-dependent action potential invasion and calcium influx into hippocampal CA1 dendrites. *Science* 268, 297–300
- 6 Magee, J.C. and Johnston, D. (1997) A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* 275, 209–213
- 7 Markram, H. *et al.* (1997) Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 275, 213–215
- 8 Bi, G.Q. and Poo, M.-M. (1998) Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *J. Neurosci.* 18, 10464–10472
- 9 Watanabe, S. *et al.* (2002) Dendritic K<sup>+</sup> channels contribute to spike-timing dependent long-term potentiation in hippocampal pyramidal neurons. *Proc. Natl. Acad. Sci. U. S. A.* 99, 8366–8371
- 10 Andreassen, M. and Lambert, J.D. (1995) Regenerative properties of pyramidal cell dendrites in area CA1 of the rat hippocampus. *J. Physiol.* 483, 421–441
- 11 Callaway, J.C. and Ross, W.N. (1995) Frequency-dependent propagation of sodium action potentials in dendrites of hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* 74, 1395–1403
- 12 Stuart, G. *et al.* (1997) Action potential initiation and backpropagation in neurons of the mammalian CNS. *Trends Neurosci.* 20, 125–131
- 13 Golding, N.L. *et al.* (2001) Dichotomy of action-potential backpropagation in CA1 pyramidal neuron dendrites. *J. Neurophysiol.* 86, 2998–3010
- 14 Golding, N.L. *et al.* (2002) Dendritic spikes as a mechanism for cooperative long-term potentiation. *Nature* 418, 326–331
- 15 Schiller, J. *et al.* (1997) Calcium action potentials restricted to distal apical dendrites of rat neocortical pyramidal neurons. *J. Physiol.* 505, 605–616
- 16 Häusser, M. *et al.* (2000) Diversity and dynamics of dendritic signaling. *Science* 290, 739–744
- 17 Frick, A. *et al.* (2003) Normalization of Ca<sup>2+</sup> signals by small oblique dendrites of CA1 pyramidal neurons. *J. Neurosci.* 23, 3243–3250
- 18 Schaefer, A.T. *et al.* (2003) Coincidence detection in pyramidal neurons is tuned by their dendritic branching pattern. *J. Neurophysiol.* 89, 3143–3154
- 19 Stuart, G.J. and Häusser, M. (2001) Dendritic coincidence detection of EPSPs and action potentials. *Nat. Neurosci.* 4, 63–71
- 20 Golding, N.L. and Spruston, N. (1998) Dendritic sodium spikes are variable triggers of axonal action potentials in hippocampal CA1 pyramidal neurons. *Neuron* 21, 1189–1200
- 21 Tsubokawa, H. and Ross, W.N. (1996) IPSPs modulate spike backpropagation and associated [Ca<sup>2+</sup>]<sub>i</sub> changes in the dendrites of hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* 76, 2896–2906
- 22 Mehta, M.R. and McNaughton, B.L. (1996) Expansion and shift of hippocampal place fields: evidence for synaptic potentiation during behavior. In *Computational Neuroscience: Trends in Research* (Bower, J., ed.), pp. 741–745, Plenum Press
- 23 Mehta, M.R. *et al.* (1997) Experience-dependent, asymmetric expansion of hippocampal place fields. *Proc. Natl. Acad. Sci. U. S. A.* 94, 8918–8921
- 24 Mehta, M.R. *et al.* (2000) Experience-dependent asymmetric shape of hippocampal receptive fields. *Neuron* 25, 707–715
- 25 Mehta, M.R. *et al.* (2002) Role of experience and oscillations in transforming a rate code into a temporal code. *Nature* 417, 741–746

- 26 Zhang, L.I. *et al.* (2003) Topography and synaptic shaping of direction selectivity in primary auditory cortex. *Nature* 424, 201–205
- 27 Engert, F. *et al.* (2002) Moving visual stimuli rapidly induce direction sensitivity of developing tectal neurons. *Nature* 419, 470–475
- 28 Movshon, J.A. *et al.* (1978) Spatial summation in the receptive fields of simple cells in the cat's striate cortex. *J. Physiol.* 283, 53–77
- 29 Mehta, M.R. and Wilson, M.A. (2000) From hippocampus to V1: effect of

LTP on spatio-temporal dynamics of receptive fields. *Neurocomputing* 32, 905–911

- 30 Euler, T. *et al.* (2002) Directionally selective calcium signals in dendrites of starburst amacrine cells. *Nature* 418, 845–852

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# An action video game modifies visual processing

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**In a recent paper, Shawn Green and Daphne Bavelier show that playing an action video game markedly improved subject performance on a range of visual skills related to detecting objects in briefly flashed displays. This is noteworthy as previous studies on perceptual learning, which have commonly focused on well-controlled and rather abstract tasks, found little transfer of learning to novel stimuli, let alone to different tasks. The data suggest that video game playing modifies visual processing on different levels: some effects are compatible with increased attentional resources, whereas others point to changes in preattentive processing.**

Will hours of playing 'Where's Waldo?' make striped sweaters jump out at you on your next trip to the department store? Would it help a baggage screener to better pick out suspicious objects from cluttered suitcases? To what extent training on one visual task transfers to other tasks is the key question in perceptual learning. In fact, although a host of experiments have shown that subjects improve with practice on a number of tasks, these same experiments often find that subtle changes of the experimental paradigm between training and testing – such as changing the shape, location or orientation of the stimuli – can have a profound effect on performance [1] (but see Ref. [2]). Such extreme specificity of learning is not of much use in the real world, where generalization and transfer from the training examples to novel scenarios, or even to different tasks, are key. In an elegantly simple and surprising paper, Green and Bavelier [3] now have provided evidence that habitual video game players (VGP) exhibit superior performance relative to non video game players (NVGP) on a set of benchmark visual tasks that tested the ability to process cluttered visual scenes and rapid stimulus sequences – skills likely to be trained by action games, which commonly require players to identify and track opponents quickly in cluttered displays and to switch rapidly between different targets. Importantly, Green and Bavelier demonstrated that this advantage is not a result of self-selection (i.e. not because subjects with superior visual abilities tend to prefer playing video games). Subjects with little or no video gaming experience showed significant

improvement on the benchmark tasks after playing just ten hours of a first-person-shooter video game, *Medal of Honor*.

## Improved object detection in clutter

What differences between NVGPs and VGPs did Green and Bavelier find, and how can those differences be interpreted? In one task, subjects had to detect a briefly flashed and masked target object (a triangle in a circle) along one of eight radial spokes made up of distractor objects (squares) emanating from the fixation point. Subjects had to report the spoke the target stimulus appeared on. VGPs showed large performance advantages over NVGPs across all distances from the fixation point that were tested (up to 30° eccentricity). Green and Bavelier interpret this difference as an enhanced allocation of spatial attention over the visual field. Previously, Ball *et al.* [4], using the same task, argued for a central role of preattentive mechanisms because target detection was found to be independent of the number of distractors, suggesting a parallel process. Interestingly, comparing subject performance with and without distractors, Ball *et al.* also found that introducing distractors decreased the diameter of the central area over which the target could be reliably detected. This is compatible with observations by Green and Bavelier in another target detection task, in which both VGPs and NVGPs appeared to process probe objects in the periphery better when there were few simultaneously presented distractors (low clutter) than when there were many (high clutter). This effect might be related to recent physiological data regarding the behavior of neurons in monkey inferotemporal cortex (IT), a brain area crucial for object recognition in the primate [5]. Neurons in IT have big receptive fields and show tuning to complex stimuli such as hands or faces. A recent study [6] showed that, in the presence of simultaneously presented clutter objects, receptive fields of IT neurons appear to shrink around an object presented at fixation. This provides a possible mechanism to increase robustness of object recognition in cluttered scenes by decreasing the region of the visual field in which distractors can interfere with the representation of an object at fixation (introducing a second object into the receptive field of an IT neuron commonly interferes with the response to the first stimulus [7]). It is interesting to note that the physiological

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