

# Synaptic modification in neural circuits: a timely action

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## Summary

Long-term modification of synaptic strength is thought to be the basic mechanism underlying the activity-dependent refinement of neural circuits and the formation of memories engrammed on them. Studies ranging from cell culture preparations to humans subjects indicate that the decision of whether a synapse will undergo strengthening or weakening critically depends on the temporal order of presynaptic and postsynaptic activity. At many synapses, potentiation will be induced only when the presynaptic neuron fires an action potential within milliseconds before the postsynaptic neuron fires, whereas weakening will occur when it is the postsynaptic neuron that fires first. Such processes might be important for the remodeling of neural circuits by activity during development and for network functions such as sequence learning and prediction. Ultimately, this synaptic property might also be fundamental for the cognitive process by which we structure our experience through cause and effect relations. *BioEssays* 24:212–222, 2002. © 2002 Wiley Periodicals, Inc. DOI 10.1002/bies.10060

## Introduction

The formation of neural circuits and the memories engrammed on them are thought to involve long-lasting modification of synaptic connections that are triggered by some kind of *experience*. How such experience is converted into these modifications is one of the most studied questions in neurobiology. It became apparent in the 1970s that synapses can be strengthened or weakened depending on the pattern of activity that they experience. In the vertebrate nervous system, a long-lasting enhancement of synaptic connections, henceforth called long-term potentiation or LTP, was first described in the hippocampus,<sup>(1,2)</sup> a cortical region strongly implicated in the processes of learning and memory formation.<sup>(3,4)</sup> Subsequently, LTP was observed in numerous other systems including the neocortex.<sup>(5–7)</sup> Conversely, most synapses that

are able to express LTP can also undergo long-term depression or LTD, a process during which the strength of a synapse becomes diminished.<sup>(8,9)</sup> In many cases, high-frequency stimulation at the presynaptic axons tends to induce LTP, while stimulation at lower frequencies favors LTD.<sup>(10,11)</sup>

To link such synaptic modifications with the highly organized processes of circuit development and function, the logic that underlies the decision whether synaptic strengthening or weakening occurs must be understood. Such logic is likely to involve the association or conjunction of input and output, i.e. presynaptic and postsynaptic activities, as has been suggested by many pioneers in the field since late nineteenth century.<sup>(12–15)</sup> This idea was further developed by Donald Hebb half century ago when he proposed the concept of cell assembly as the basis of *perceptual integration* and learning in the cortex.<sup>(15)</sup> By cell assembly, Hebb imagined a circuit of interconnected neurons that is capable of responding to specific external input with a sequence of firing activity. This activity may reverberate within the circuit for hundreds of milliseconds, the time period of a single “conscious content”, and hence constitute a short-term “memory trace.” Moreover, the activity may induce long-lasting cellular changes within the assembly, which in turn reinforce the specific connections and facilitate re-activation or “retrieval” of the previously “learned” activity patterns. In other words, the transient memory trace becomes converted into a permanent engram. In his “neurophysiological postulate”, Hebb envisioned a cellular mechanism for such positive-feedback process: “When an axon of cell A is near enough to excite a 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 efficiency, as one of the cells firing B, is increased.” Essentially what Hebb was postulating is that correlated presynaptic and postsynaptic activity would induce synaptic strengthening. As we will see in the next section, he was thus anticipating to a remarkable degree and on purely theoretical grounds the outcome of a series of recent experiments that have addressed the question of the role of the temporal structure of the activity pattern for synaptic modifications.

Central to Hebb’s postulate is an element of timing—the synaptic connection is strengthened only if cell A “takes parts in firing” cell B. Early pioneering studies on LTP indeed indicated that the temporal order of presynaptic and postsynaptic activation might be of crucial importance for the modification of synapses.<sup>(16–18)</sup> However, most previous

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studies based on this postulate interpreted it as a requirement of the “coincidence” of presynaptic and postsynaptic activity for synaptic modification,<sup>(7,19,20)</sup> a notion that became popularized by the famous mnemonic: “cells that fire together, wire together”.<sup>(21)</sup> A synapse that showed this coincidence requirement for its modification was subsequently coined a *Hebbian synapse*. The introduction of the Hebbian synapse has proved extremely valuable for theoretical studies of neural network models<sup>(19,22–24)</sup> and has stimulated the design of specific experiments. For instance, the so-called “pairing protocol” to induce LTP, i.e. presynaptic stimulation coupled with prolonged postsynaptic depolarization,<sup>(7,25–27)</sup> can be seen as a brainchild of the Hebbian synapse concept.

### Spike-timing dependent synaptic modification

In the conventional concept of Hebbian synapse as well as the classical “pairing” experiments, the property of coincidence or “firing together” was examined with a fairly low temporal resolution—in the order of seconds instead of milliseconds typical for the generation of neuronal action potentials, or *spikes* (i.e., the process of cell A firing cell B). In the past few years, a series of experiments, using techniques that allow for direct activation of temporally correlated presynaptic and postsynaptic action potentials (spikes) with millisecond precision, have revealed a new and maybe more interesting picture: instead of mere coincidence, the precise timing of presynaptic and postsynaptic spikes was shown to determine both the extent and polarity of synaptic modification.<sup>(28–33)</sup> The decisive breakthrough came with studies performed in rat brain slices, in which LTP was induced when postsynaptic BACK-PROPAGATING SPIKES<sup>(34,35)</sup> (see Glossary, Box 1) followed presynaptic activation (also referred to as positive SPIKE-TIMING) by 10 milliseconds, whereas LTD was induced when the temporal order of the spikes was reversed (negative spike-timing).<sup>(28)</sup>

The observation of such spike-timing-dependent plasticity (STDP) has shown that the detailed temporal structure of neural activity can be critical for the occurrence, extent and polarity of synaptic modification and suggests redefining the notion of “coincidence” with a millisecond precision. In cultured hippocampal glutamatergic neurons,<sup>(32)</sup> the range of spike-timing for effective synaptic modification (here referred to as the “critical spike-timing window”) was shown to be of about 50 milliseconds (Fig. 1). If postsynaptic spiking occurred too early or too late (by just tens of milliseconds) relative to the presynaptic activity, the synapse was not modified. In addition, the width of the transition zone from maximal LTP to maximal LTD was less than 5 milliseconds. Therefore a synapse can discriminate fine temporal differences in its presynaptic and postsynaptic activity. Similar asymmetric windows have been found in many other *in vitro* and *in vivo* systems.<sup>(31,33)</sup> Possible cellular mechanisms underlying STDP and the asymmetric window is the subject of an article by Chris Rongo<sup>(101)</sup>

### Box 1: Glossary

**BACK-PROPAGATING SPIKE**—Action potential that is initiated at the soma or axon and propagates back into the dendrites, i.e. opposite to the classical direction of action potential propagation.

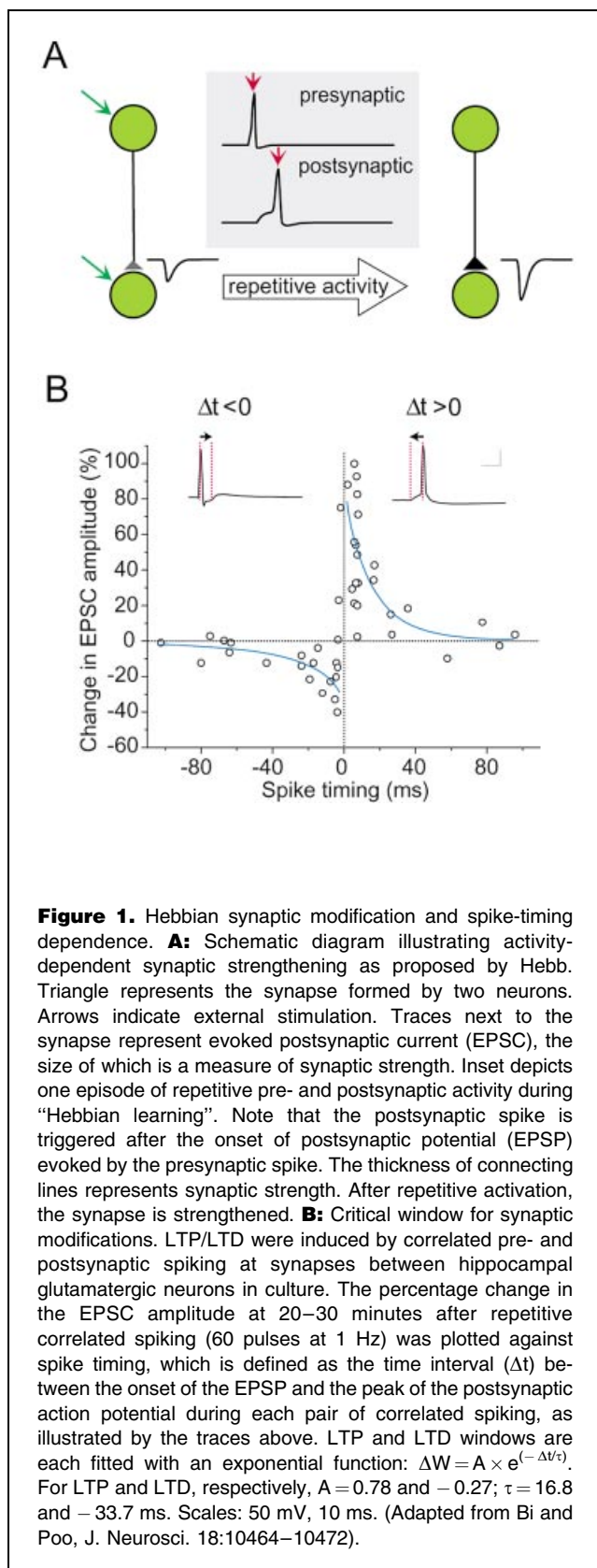
**EXCITATORY POSTSYNAPTIC POTENTIAL (EPSP)**—Depolarization of the membrane potential of the postsynaptic cell as consequence of the activation of a synapse using an excitatory neurotransmitter (usually glutamate in vertebrate central nervous system) that binds to and opens postsynaptic receptor channels. The transmitter is excitatory when the potential at which the current flow through the activated receptor channel reverses is more positive than the threshold for action potential generation.

**POLYSYNAPTIC CURRENT**—Synaptic current evoked by activating a neuron(s) that connects to the postsynaptic cell indirectly via a POLYSYNAPTIC PATHWAY(S). A polysynaptic current often consists of multiple components, each with a distinct transmission delay.

**POLYSYNAPTIC PATHWAY**—A pathway along which nerve impulses transmit across multiple synapses. In culture, one such pathway may be comprised of a chain of serially connected single neurons. A single input stimulus may result in sequential excitation of each neuron in the chain.

**SPIKE-TIMING**—A quantitative measure of the relative timing between presynaptic and postsynaptic activation. Here it is defined as the time interval from the onset of the input EXCITATORY POSTSYNAPTIC POTENTIAL (EPSP) to the peak of the postsynaptic spike, both of which can be measured at the soma of the postsynaptic cell. A positive spike-timing thus means that the postsynaptic spiking follows the presynaptic input, and a negative spike-timing means the opposite.

(see also Box 2). Moreover, other types of synapses may be modified according to distinctly different rules. A particularly intriguing rule was uncovered at synapses between parallel fibers and Purkinje-like cells in the cerebellum-like structure of electric fish. As with hippocampal synapses, these synapses were modified by correlated presynaptic and postsynaptic spiking activity, but the modifications were of opposite polarity: positive spike timing resulted in LTD while negative timing led to LTP.<sup>(30)</sup> This opposite polarity may be related to the fact that the postsynaptic Purkinje-like cell comprises an inhibitory rather than an excitatory projection neuron. In addition, in rat somatosensory cortex, excitatory neurons at different layers display markedly different modification windows. In somatosensory cortex, synapses between layer V pyramidal neurons exhibit a temporal requirement for LTP and LTD similar to



### Box 2. Cellular basis of STDP

The cellular mechanisms of STDP are not completely understood. However it is generally believed that a transient increase of postsynaptic intracellular  $\text{Ca}^{2+}$  plays a central role, and down-stream to  $\text{Ca}^{2+}$ , multiple protein kinases and phosphatases signal for the cellular changes in presynaptic and/or postsynaptic neurons.<sup>(20,52,97)</sup> Indeed, in dendritic spines of cortical neurons, supra- and sublinear summation of  $\text{Ca}^{2+}$  transients depends on the relative timing of synaptic activation and back-propagating spiking.<sup>(98)</sup> In many cases the induction of LTP and LTD depends critically on the activation of so-called NMDA type glutamate receptors that appear to act as a molecular coincidence detectors, by virtue of their particular property that channel opening occurs only when glutamate binds to the receptor AND when  $\text{Mg}^{2+}$  ions blocking the channel pore are removed by coincident depolarization. The degree of channel opening will then determine the amount of calcium passing through the pore, which in turn seems to be critical for the polarity of the synaptic modification.<sup>(99,100)</sup>

that shown in Fig. 1;<sup>(28)</sup> synaptic inputs from layer IV to layer II/III, which are otherwise similar, show a broader depression window.<sup>(33)</sup> In contrast to these synapses, synapses between layer IV spiny stellate neurons exhibit a totally different, i.e. symmetric, modification window: independent of the temporal order of presynaptic and postsynaptic activity, only depression was observed.<sup>(36)</sup> The diversity of spike-timing windows for synaptic modification most likely reflects the complexity of the respective underlying cellular mechanisms and is certainly related to the different computational tasks of these synapses in neural information processing. The rest of this article will focus on the asymmetric spike-timing window that appears to be typical for most synapses between pyramidal neurons (Fig. 1).

### Temporal asymmetry, causation detection, and prediction

The temporally asymmetric spike-timing window for synaptic plasticity has recently become a subject of many detailed theoretical studies.<sup>(37–51)</sup> In addition to the conventional interpretation of the Hebbian synapse that emphasizes the association between two concomitant events,<sup>(19,24)</sup> the asymmetry in the window highlights the significance of temporal order, and possibly even the causal relationship between two events.<sup>(20,52–54)</sup> A requirement of causality was already implied in Hebb’s original statement: a synaptic input was to be strengthened only when it “takes part in firing” the postsynaptic cell. It is worth noting that the 20-millisecond

“potentiation window” matches the duration of a typical excitatory synaptic potential. When a postsynaptic spike occurs within this window following a synaptic input, it is in fact very likely that this input has contributed to the generation of the spike. Such inputs being potentiated (Fig. 1) suggests that the synapse has the ability to act also as a kind of “causation detector”, rather than a mere “coincidence detector” of presynaptic and postsynaptic activity. If the “coincident” activity occurs in the anti-causal order (i.e., postsynaptic spiking preceding the presynaptic input), the synapse will be weakened as shown by the left half of the spike-timing window (Fig. 1). This complementary “depression window” is valuable from a computational point of view because it not only reinforces the causation detection, but also helps ensure the stability of memory storage in a network.<sup>(22,53,55,56)</sup> Theoretical studies on the spike-timing-dependent learning rule have shown that the balance of integrals of the potentiation and depression windows (a property called “self-normalization”) is important for a balanced synaptic competition in a neural network.<sup>(40,41,45,46)</sup>

The notion that an asymmetric synaptic plasticity mechanism can be seen as part of a causation-detection device has some additional implications. As discussed below, spike-timing-dependent plasticity rules are well suited for creating neural networks with predictive behavior, which represents an important practical aspect of interpreting the world as causally structured. Furthermore, we may ask whether such asymmetric plasticity rule is in fact a prerequisite for our perception of the world as causally structured (i.e. built stringently upon cause–effect relations—see Box 3 for an explanation). It would be intriguing to discover the behavioral and cognitive consequences of reversing the normal polarity of synaptic modification (i.e. LTP into LTD and vice versa). Eventually, molecular techniques may allow this issue to be addressed experimentally.

To illustrate the implications of STDP, and especially of its temporal asymmetry, for the functioning of neural circuits, it might be worthwhile examining a few very simple systems that may be regarded as elementary “subcircuits” of more complex networks. One of the simplest systems possible consists of two symmetrically interconnected neurons A and B, each of which is activated by an external event *a* or *b*, respectively (Fig. 2A). If event *b* always occurs “immediately” after event *a* so that neurons A and B are consistently activated in this specific temporal order, the synapse  $S_{A \rightarrow B}$  will be eventually potentiated whereas the synapse  $S_{B \rightarrow A}$  will be depressed. Thus the initial symmetry in the connectivity is broken: cell A will have stronger influence on the firing of cell B than (cell) B on the firing of (cell) A. In an extreme case,  $S_{B \rightarrow A}$  will be so weak that activation of neuron B will have little effect on neuron A, whereas  $S_{A \rightarrow B}$  will be strong enough so that activation of neuron A alone will fire neuron B. Thus an association between the two events might be established in

such way that the network will *predict* the occurrence of event *b* when event *a* has occurred. Meanwhile, the depression of  $S_{B \rightarrow A}$  implies that the probability of the reverse event series  $b \rightarrow a$  is below that of random occurrence. This scenario is of course reminiscent of the well-characterized phenomenon of classical conditioning, for which the onset of the conditioned stimulus requires an unconditioned stimulus occurring shortly after.<sup>(57)</sup> However, the time scale of the spike-timing window (tens of milliseconds) is at least an order of magnitude too small to explain the most commonly observed behavioral conditioning which usually involves a fraction of a second to several seconds. One possibility is that synapses involved in the conditioning may employ cellular processes of slower kinetics to allow for the interaction between presynaptic and postsynaptic activity with longer intervals.<sup>(58)</sup> Alternatively, recurrent networks may allow persistent activity or sequential firing in many neurons following an input stimulus, thereby effectively extending the time scale of interaction between input stimuli.<sup>(53,59,60)</sup> In this scenario, synapses with narrow spike-timing windows can still be involved in associative learning of event sequences with longer intervals.

Let us now consider a slightly more complicated system consisting of three neurons (Fig. 2B). We assume an asymmetric initial condition: the connection  $S_{A \rightarrow C}$  is initially weak (subthreshold) whereas connections  $S_{A \rightarrow B}$  and  $S_{B \rightarrow C}$  are both strong (suprathreshold). This allows input into neuron A to result in firing of neuron C via the already established  $A \rightarrow B \rightarrow C$  pathway. With such sequential activation of cells A, B, and C, the subthreshold connection  $S_{A \rightarrow C}$  would now be activated right before firing of neuron C, thus leading to strengthening of this synapse. Eventually  $S_{A \rightarrow C}$  may be strengthened to the point that its activation alone is sufficient to fire cell C. Then because the  $A \rightarrow C$  pathway is shorter than the  $A \rightarrow B \rightarrow C$  pathway,  $S_{B \rightarrow C}$  will be activated *after* the firing of C by  $S_{A \rightarrow C}$  and will thus be depressed. Thus the original longer pathway of circuit activation  $A \rightarrow B \rightarrow C$  will eventually be replaced by the shortcut  $A \rightarrow C$ . For some neural circuits, such a process implies instability that is not desirable and may be counteracted by other network mechanisms. In other cases, the instability itself may be a useful feature because, in a sense, the shortened  $A \rightarrow C$  pathway carries out the same function as the longer  $A \rightarrow B \rightarrow C$  pathway but more rapidly. One might say that the  $A \rightarrow C$  pathway now *predicts* the supposedly incoming commands from neuron B. In other words, this simple network in effect carries out a logic operation that short cuts the syllogism—if  $A \rightarrow B$ , and  $B \rightarrow C$  then also  $A \rightarrow C$ . More generally, the arbitrary units A, B, and C would not need to be single neurons, but may represent groups of neurons or cell assemblies.

We would like to stress that the examples discussed above are simplified to the point that may seem somewhat trivial. Yet, we think they illustrate how the “low-level” rules of synaptic modification may introduce a specific logic into

### Box 3. Appendix: a neurobiological correlate for the philosophical critique of the principle of causality?

The temporal asymmetry of the STDP found at many synapses seems to reflect the causal dependence of the generation of an action potential in the postsynaptic cell on prior presynaptic firing. In this context, we spoke of a kind of cellular “causation detection device”: when two events *a* and *b* activate in close succession two connected units *A* and *B*, then following the STDP “algorithm” the connection  $A \rightarrow B$  becomes strengthened. The strength of this connection may thus be seen as representing the degree of probability that two events occur in succession. In an extreme case, such probability may approximate 1, that is when event *b* succeeds event *a* with necessity, which means nothing else but that event *a* and *b* are causally linked (see below for the definition of causality according to Hume).

Thus, synaptic connections that obey temporally asymmetric STDP can be used to represent the pairing of causes and their respective effects. This may then suggest that the cognitive process by which we structure our experience in cause and effect relations ultimately depends on, at the cellular level, the property of temporal asymmetry of STDP. Such considerations are supported by the observation that temporally asymmetric STDP can endow the neural networks with predictive power, i.e. with the ability to predict upcoming events or locations along a familiar series of events or locations, respectively. Generally spoken, temporally asymmetric STDP seems to introduce an element of directionality in the relation between two cognitive contents. Two aspects deserve mentioning here: (i) in order to establish such directionality, any two contents must occur in the respective temporal/spatial order, preferably repeatedly, and (ii) although the temporal/spatial order of any two cognitive contents determines the actual directionality of their connection, it is the temporal asymmetry of the STDP window that governs the process of connecting itself. Essentially, STDP represents the expectation that any event must be preceded by another. That means the synaptic modification rule introduces an a priori element, i.e. an element that itself is not dependent on prior experience, at least insofar that such rule itself is not subject to change due to prior experience.

Given the pivotal role that the concept of causality plays in both our everyday thinking as well as in scientific reasoning, one must wonder about its origin. Naively, the notion of causality may be thought of being derived from observation, for instance by observing the repeated conjunction of two events, one of these being assigned as the cause and the other as the effect. Yet that this can't be the case was already recognized by the Scottish philosopher David Hume. In his “Treatise on Human Nature” (Hume, 1739), Hume suggested that the idea of causality is based on three criteria: (i) Contiguity (in time and space) of cause and effect, (ii) priority (of the cause vs. the effect) and (iii) a “necessary connection” between the both. He thought that, while the first two criteria might indeed be derived from observation, the third criterion, i.e. that of the necessary connection between cause and its effect, could not be directly found in the things that we observe. As often we might see an event *b* follow an event *a*, there was no proof of necessity therein for *b* to follow *a*. Following herein Hume, Immanuel Kant recognized that the idea of the “necessary connection” can indeed not be derived from experience, but—as he states in his “Critique of Pure Reason” (Kant, 1787)—instead serves as “the ground of experience itself and consequently precedes it a priori”. For Kant then “the principle of cause and effect is the principle of possible experience, that is, of objective cognition of phenomena, in regard to their relations in the succession of time”. In other words, according to Kant, the mind can be considered as structuring experience using the concept of causality as an organizing principle, rather than the other way round according to which experience would teach us the concept of causality.

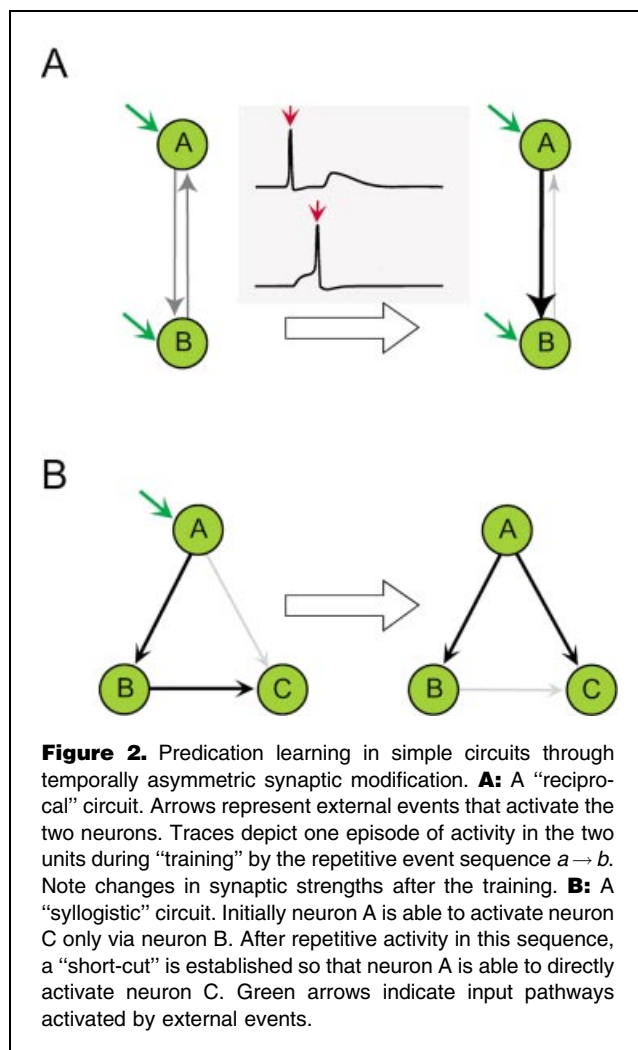
What is the neurobiological basis for such organizing principle? As we have mentioned above, STDP introduces an a priori momentum into the process by which two cognitive contents are connected. By being temporally asymmetric it introduces furthermore a directionality that is typical of cause and effect relations. Thus it seems that STDP is characterized by traits that make it an attractive candidate serving as an essential building block for mental category of causality.

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Kant I. (1787). *Critique of Pure Reason*. Translated by Smith NK (1969). Unabridged edition.

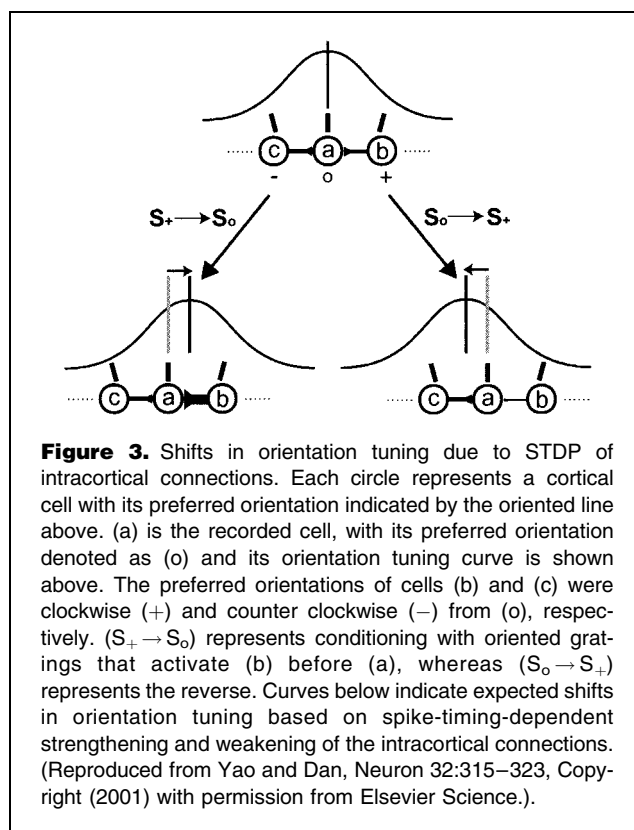
network operations. Indeed the behavior of much more complex systems, such as the mammalian hippocampus, where synapses exhibit the asymmetric modification window, follows principles similar to these simple networks. In the CA1 and CA3 region of the hippocampus, some principle neurons behave like “place cells”, with each place cell actively firing action potentials only when the animal is in a particular area(s),

the “place field” of the neuron, within its environment.<sup>(61,62)</sup> Interestingly, these place fields show significant asymmetric expansion as the animal familiarizes with the environment.<sup>(44,63,64)</sup> Such expansion can be explained by a STDP-based network mechanisms<sup>(39,44)</sup> analogous to the simple examples discussed earlier. When the animal moves through adjacent locations *a* and *b*, corresponding place cells



A and B will become activated sequentially. In reality, A, B may represent many cells that fire at locations  $a$  and  $b$ . Following the same principle of STDP, however, one can expect that, after repeated experience of passing through a *familiar* path (say from  $a$  to  $b$ ), asymmetric connections among place cells (i.e. neuron A being functionally connected to neuron B, but not the other way round) may be established. Then if the animal takes the same path, neuron B may start to fire already when the animal is still in  $a$ , prior to the animal entering of its original place field. Thus the place field for B apparently expands against the direction of the familiar route, to include both locations  $a$  and  $b$ . In other words, through STDP and subsequently formed asymmetric connections, the sequential firing of A and B will *predict* the upcoming positions along the path. One can further extend the path to envision more elaborate navigational maps that have been shown to form in modeled networks of place cells when the asymmetric synaptic learning rule is implemented.<sup>(39)</sup>

Asymmetric plasticity has also been observed recently in the primary visual cortex. Many neurons in this cortical area display a property called orientation selectivity, i.e. when stimulated with gratings of various orientations they will respond most vigorously at a certain optimal orientation. Yao and Dan<sup>(65)</sup> found that, when the optimal orientation was repetitively paired with another suboptimal orientation, the orientation tuning of the neuron was shifted (Fig. 3). Importantly the direction of the shift in orientation tuning was critically dependent on the temporal order in which the two orientations had been presented. When the suboptimal orientation was presented before the optimal one, the tuning curve was shifted towards the suboptimal orientation. The reverse shift occurred when the presentation of the stimuli was in the opposite order. Moreover, the time interval effective for this plasticity was in the range of  $\pm 40$  milliseconds, thus intriguingly resembling the critical time window of synaptic modifications described above. The most parsimonious explanation is that the shift in orientation can be again accounted for by STDP. Interestingly, a similar shift in orientation tuning was also revealed at the level of whole orientation maps by optical imaging.<sup>(66)</sup> Finally, shifts in orientation selectivity have been observed also in human subjects by psychophysical experiments. Based on the apparent similarity of this behavior with that of hippocampal networks, it was hypothesized that a kind of sequence learning might also occur in visual cortex.<sup>(65)</sup>



Taken together, the temporal asymmetry of the synaptic learning rule may be considered as the very basis of the fundamental process of prediction operating in different levels of network organization. The predictive nature of neural circuits in turn allows a more active interaction between an animal and its external world.

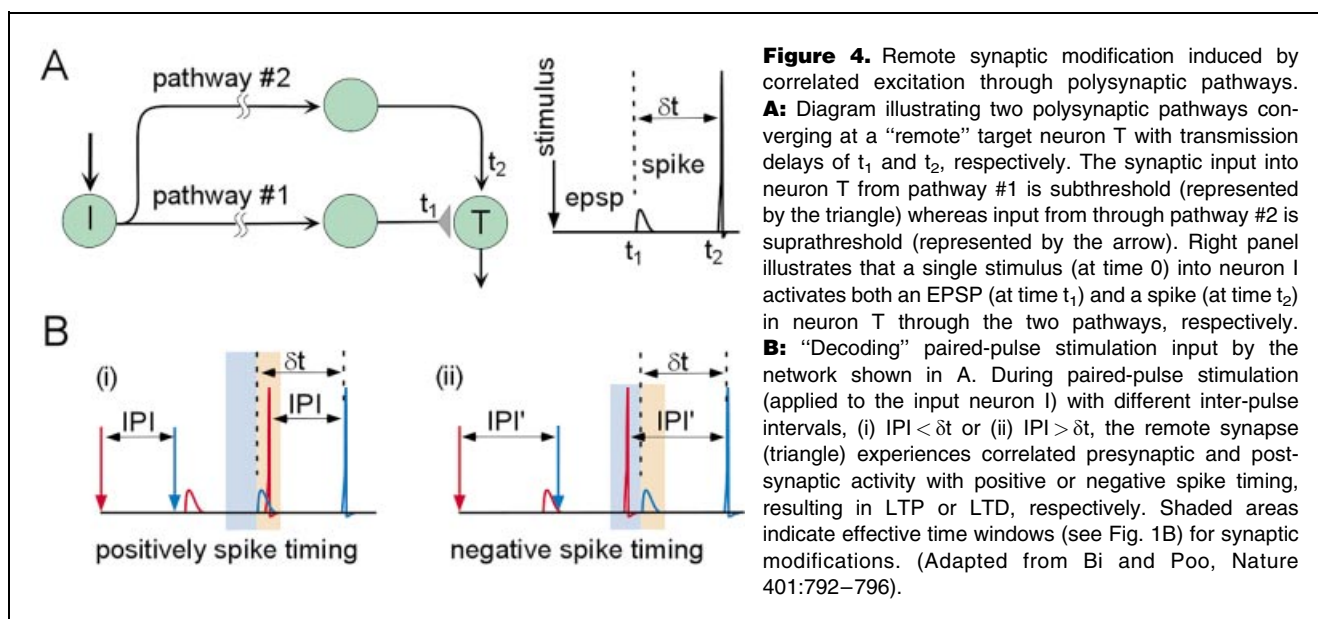
### Distributed, remote synaptic modifications in neural circuits

Networks of cultured hippocampal neurons have allowed us to explore in more detail some of the functional consequences of the temporally asymmetric window for synaptic modification in neural assemblies of still manageable size. In such networks, suprathreshold connections between single neurons are encountered relatively frequently. Therefore stimulating a randomly chosen “input” neuron within the network results eventually in the activation of multiple POLYSYNAPTIC PATHWAYS. Thus, from another cell in the network, one can record POLYSYNAPTIC CURRENTS consisting of multiple current components that occur with varied time delays corresponding to different pathways that connect the sites of stimulation and recording.<sup>(67)</sup> Such polysynaptic delay comprises the latency of transmission at each synapse and the time required for the generation and propagation of the action potential. These sum to several milliseconds per synapse along any given pathway.

One interesting phenomenon found in these cultured networks is that repetitive paired-pulse stimulation of the “input neuron” sometimes results in distinct, long-lasting changes in the pattern of recorded polysynaptic currents. These changes include appearance of new polysynaptic current components, disappearance of previously existing components, or significant changes in the probability of occurrence of certain

components.<sup>(67)</sup> These changes can be attributed to modifications of “remote” synapses (with respect to the site of input) in the network, leading to changes in the probability of activating particular polysynaptic pathways. (Fig. 4) depicts a schematic example of such a network with two polysynaptic pathways converging onto a remote target neuron T. The input arising from one pathway is subthreshold whereas the other input is suprathreshold. Thus stimulation of input neuron I results in the generation of both an EXCITATORY POSTSYNAPTIC POTENTIAL (EPSP) and a spike at neuron T, separated by a time interval equal to the differential delay between the two pathways. When the input neuron is activated by a paired-pulse then, depending on the inter-pulse interval, activity along different pathways may coincide at neuron T within the critical window for synaptic modification. Following the principle of STDP discussed above, we can expect potentiation or depression of the subthreshold remote synapse, depending on the “local” spike timing. In general terms, a given pattern of input stimuli will result in coincident activity at multiple remote synapses distributed throughout the network; the subsequent modifications of these synapses depend on the spatiotemporal pattern of the input as well as the pathway architecture of the network. The distributed synaptic modifications will in turn lead to functional remodeling, i.e. changes in the activation pattern of neurons and pathways, within the circuitry.

The essence of the network structure discussed above is that the polysynaptic pathways function as “delay-lines”, reminiscent of axonal delay-lines proposed for the auditory system and used in certain neural network models.<sup>(68–71)</sup> Through sequential activation in such delay-lines, input stimuli that are temporally spread can be “concentrated” into a relatively narrow window of integration time on certain nodes



distributed in a network. In other words, delay-line architecture provides a straightforward means for converting temporal information inherent within natural inputs into a spatially distributed representation, hence allowing a network to process such information according to simple local rules. This property has been explored in many neural network models for sequence processing and generation and has been used in applications such as speech recognition.<sup>(72–76)</sup>

In contrast to the networks of cultured neurons, suprathreshold connections are rarely encountered between pyramidal neurons in vivo. However, polysynaptic pathways may exist in the brain in the form of connected assemblies. For example, in the so-called “synfire” model,<sup>(77)</sup> synchronous spiking activity propagates from one group of neurons to another, forming “synfire chains” analogous to the polysynaptic pathways in culture. Theoretical studies have shown that synchronous spiking may propagate stably as tight “pulse packets” along a synfire chain while preserving the accuracy of spike timing.<sup>(78,79)</sup> Experimentally, synchronous firing and traveling waves have been observed in many areas of invertebrate and vertebrate brains,<sup>(80,81)</sup> indicating the existence of biological mechanisms for maintaining coherence in neuronal firing. It is conceivable that certain input stimuli might trigger neural activity that propagates and even reverberates along specific pathways—series of subpopulation of neurons—in a recurrently connected network.<sup>(82,83)</sup> Such propagation and reverberation resemble the cell assemblies that Hebb envisioned as the neural correlate of elementary thought process.<sup>(15)</sup> Finally, the interaction between different pathways in real neural networks will be further complicated by the dynamic modulation of synaptic strength that results from short-term plasticity, which itself is highly dependent on the temporal structure of activity.<sup>(84)</sup> Thus, ultimately, the functional configuration of a network, i.e. its pathways and assemblies, can no longer be considered as static objects, but must be seen as highly dynamic.

### Development of cortical circuitry: extrinsic instruction and intrinsic rules

In the previous sections, we have discussed how spatiotemporal patterns of input activity may be laid down in the form of spatially distributed synaptic modifications, ultimately resulting in functional remodeling of a neural circuit during learning and memory formation. We now consider whether the same principles underlie the activity-dependent refinement of the highly ordered neuronal circuitry during development.<sup>(85,86)</sup> Firstly, the optic tectum of developing *Xenopus* tadpoles was one of the first systems in which STDP was observed.<sup>(31)</sup> Secondly, theoretical studies have elegantly demonstrated that various formulations of Hebbian rules can lead to the formation of ocular dominance or orientation columns.<sup>(23,55,87)</sup> Thirdly, STDP-based network models have been shown to simulate the development of feature-selective maps in the

cortex.<sup>(49,88)</sup> These theoretical works are based on the premise that neural activity would play an *instructive* role in the formation of neural circuits during development.<sup>(89,90)</sup> *Instructive* means that the spatiotemporal pattern of neural activity specifies which neurons become interconnected and to what extent. Alternatively, activity might play a merely permissive role, in which case it might be required for the development of the circuitry without specifying which connections are to be formed.<sup>(91)</sup> The issue of whether neural activity indeed guides the formation of neuronal circuitry in an instructive fashion is not resolved at present. Recent experiments have further deepened the puzzle by providing evidence in favor of activity-independent mechanisms for the shaping of neural circuits in experimental paradigms that have previously served as classical examples for activity-dependent mechanisms.<sup>(92–94)</sup>

Striking evidence for an instructive role of neural activity in neural circuit formation, however, has come from a quite unique experimental preparation. When auditory input fibers projecting into the auditory thalamic relay are lesioned prior to the time when the axons from the relay have reached their target in the cortex, the cortical area that normally would process auditory input will now become responsive to visual stimulation.<sup>(91)</sup> This is due to the fact that a subpopulation of retinal axons that convey visual input takes over the space left by the degenerated auditory fibers in the auditory thalamic relay. If the hypothesis of an instructive role of neural activity in the formation of cortical circuits were to be correct, one would expect that cortical wiring would be fundamentally different depending on the source of sensory input. Indeed functional and anatomical evidence from these studies point to substantial differences in the formation of horizontal connections within normal and “rewired” auditory cortex.<sup>(95)</sup> Visually activated primary auditory cortex (rewired A1) was shown to resemble primary visual cortex (V1) rather than control A1<sup>(95)</sup> regarding its long-range horizontal connections. In behavioral experiments, ferrets with rewired A1 appeared to interpret light stimuli that activated the auditory cortex as visual and not as auditory indicating a remarkable shift in the sensory quality perceived by the animal using the same piece of cortex.<sup>(96)</sup> These data suggest that a given sensory modality is to a large extent determined by the spatiotemporal pattern of activity that it receives from its corresponding sense organ rather than by intrinsic factors.

We will now consider these findings from the perspective of the synaptic plasticity mechanisms discussed above. In normal animals, different types of sensory inputs would produce different sets of neural spike patterns in their corresponding thalamic relays, which in turn may result in the modification of different sets of *remote* synapses within their cortical projection areas. In one case, this might result in a patchy distribution of long-range horizontal connections (as seen in V1) and, in the other case, in a more radial

connectivity (as seen in A1). To produce distinct types of functional organization, patterns of input activity have to bear a characteristic signature. Hence it will be of great interest to characterize the differences in the normal firing patterns between thalamic projection neurons located in auditory and visual thalamic relays and understand how these differences might account for the development of distinct functional organization in normal A1 and V1.

The findings in the visual cortex provide evidence that cortical processing varies in a way that is to a considerable extent determined by the incoming data-to-be-processed, i.e. their spatio-temporal structure. Thus, prior to functional specialization, the different cortical areas might be seen as *tabula rasa* in that their circuitry becomes molded according to the spatiotemporal structure of their input. Ironically we might say then these findings vindicate an “empiricist” viewpoint according to which “*there is nothing in the mind (read cortex for mind) save that which is attained through the senses (read spatiotemporal structure of the input for attained through the senses)*”. Yet the mode by which the spatiotemporal structure of the input exerts its influence on cortical networks is crucially dependent on the structure of the synaptic modification “algorithms” that introduce an a priori element (insofar as these “algorithms” are not subject to modification by experience).

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