Metaplasticity: the plasticity of synaptic plasticity

Wickliffe C. Abraham and Mark F. Bear

In this paper, we review experimental evidence for a novel form of persistent synaptic plasticity we call metaplasticity. Metaplasticity is induced by synaptic or cellular activity, but it is not necessarily expressed as a change in the efficacy of normal synaptic transmission. Instead, it is manifest as a change in the ability to induce subsequent synaptic plasticity, such as long-term potentiation or depression. Thus, metaplasticity is a higher-order form of synaptic plasticity. Metaplasticity might involve alterations in NMDA-receptor function in some cases, but there are many other candidate mechanisms. The induction of metaplasticity complicates the interpretation of many commonly studied aspects of synaptic plasticity, such as saturation and biochemical correlates.

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ACTIVITY-DEPENDENT modifications of synaptic efficacy are fundamental to the storage of information in the brain. Yet this may not be the only way by which synaptic activity can leave a lasting trace. Consider the effects of a short burst (30 Hz, 150 ms) of synaptic stimulation in area CA1 of the hippocampus. By itself, such a burst causes only a transient short-term potentiation (STP) of evoked responses that decays rapidly back to baseline[1]. However, long-lasting effects of this seemingly innocuous activity become apparent during subsequent attempts to induce synaptic plasticity. These effects include both an inhibition of long-term potentiation (LTP; Ref. 2; Fig. 1), and a facilitation of long-term depression (LTD)[3]. Similar examples can be found in a variety of neural systems, all indicating that synaptic plasticity can be modulated, sometimes dramatically, by prior synaptic activity. We call this plasticity of synaptic plasticity 'metaplasticity', which corresponds in meaning to terms such as 'metacognition' (knowledge about one's cognitions) and 'meta-analysis' (a higher-order analysis of the results from many other studies or analyses). In the present case, the prefix 'meta-', Greek for 'beyond' or 'above', is used to indicate a higher level of plasticity, expressed as a change or transformation in the way synaptic efficacy is modified. An understanding of metaplasticity might yield new insights into how the modification of synapses is regulated and how information is stored by synapses in the brain.

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What phenomena fall within our conceptualization of metaplasticity? At this early stage we wish the definition to be inclusive rather than exclusive. We suggest the following guideline: metaplasticity has occurred if prior synaptic or cellular activity (or inactivity) leads to a persistent change in the direction or degree of synaptic plasticity elicited by a given pattern of synaptic activation. Metaplasticity is most obvious when it occurs without concurrent changes in synaptic efficacy but, in principle, metaplasticity and synaptic modifications can also be induced simultaneously by the same synaptic activity.

In this paper, we briefly review the evidence for metaplasticity and discuss some likely mechanisms. Acknowledging that metaplasticity occurs might substantially alter how the lasting effects of synaptic activation are interpreted.

Metaplasticity of LTP

In an early study, Coan *et al.*[4] found that LTP could not be produced in the CA1 region when hippocampal slices were bathed in a nominally Mg^{2+}-free medium. This effect was considered paradoxical at the time because the expectation was that removing Mg^{2+} from the extracellular solution should promote LTP induction by increasing the conductance of NMDA channels. Instead, it appeared that the activation of NMDA receptors by baseline test pulses actually inhibited subsequent LTP induction. More recent studies in the CA1 region have confirmed this basic effect. In a series of experiments by Huang *et al.*[2], induction of LTP by a strong tetanus was inhibited if weak tetani were previously delivered to the same Schaffer collateral input pathway. The effect was input-specific and lasted at least 30 min, but less than an hour. This inhibition of LTP was found to be due to activation of NMDA receptors because LTP occurred normally when the NMDA antagonist, aminophosphonopentanoate (AP5) was present during the weak tetani, and iontophoretic application of NMDA to the slice could substitute for the weak tetanic stimulation. Similar results have been reported by several groups, which have shown that prior synaptic activity can inhibit the induction of subsequent LTP by high-frequency stimulation[5–8].

Taken together, the data suggest that low-level activation of NMDA receptors in the CA1 region induces a covert synaptic change (metaplasticity) that inhibits the subsequent induction of LTP. The inhibition of LTP in these experiments is not absolute, however, because it can be overcome by stronger tetanic stimulation[2]. Thus, prior stimulation appears to raise the stimulation threshold for LTP, rather than block plasticity *per se*.

In a situation similar to that in the CA1 region, a brief train of 5 Hz stimulation in the dentate gyrus

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(which produces no persistent changes in the evoked synaptic responses) also inhibits LTP induced by strong tetanic stimulation[9]. Surprisingly, however, the same 5 Hz 'priming' stimulation can facilitate LTP when evoked by a near-threshold tetanus containing fewer trains[10]. The explanation for this apparent discrepancy lies in the fact that LTP induction in the lateral perforant path under normal conditions varies as an inverted U-shaped function of the number of stimulus trains (Fig. 2). Prior priming stimulation shifts the whole LTP induction function to the left, so weak stimulation is more likely, and strong stimulation is less likely, to produce LTP. The complexity of these data emphasizes the need to test a wide range of tetanization protocols to characterize fully the effects of prior activity on LTP induction.

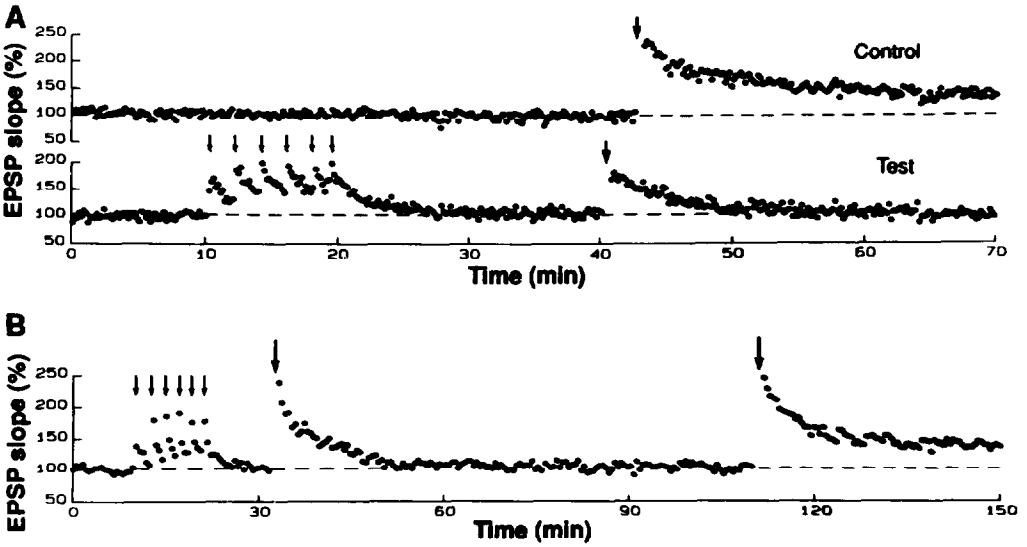

Fig. 1. ***Effect of prior stimulation on long-term potentiation (LTP) in area CA1 of the hippocampus.*** **(A)** *The population excitatory postsynaptic potential (EPSP) was recorded and two separate pathways (control and test) were stimulated alternately. At the times indicated by the small downward arrows, weak tetani (30 Hz, 0.15 s) were delivered to the test pathway. Although this stimulation did not produce a lasting change in synaptic effectiveness, it did inhibit induction of LTP by a strong tetanus delivered 20 minutes later (indicated by the large downward arrow). LTP on the control path was unaffected.* **(B)** *The inhibition of LTP caused by prior stimulation was transient, lasting no more than about an hour.* Figure adapted, with permission, from Ref. 2.

Metaplasticity of LTD

Christie and Abraham[9] described a form of homosynaptic LTD, termed 'associative' LTD, that occurs in the lateral perforant path when low-frequency stimulation of this pathway is delivered out-of-phase with brief high-frequency trains delivered to the medial perforant path. In this study, associative LTD only occurred, however, if prior 5 Hz priming stimulation was given to the lateral perforant path; no associative LTD was observed without priming stimulation. Consistent with the other metaplasticity results described thus far, the priming effect was found to be input specific and to involve activation of NMDA receptors during the priming stimulation. The priming effect in this case was unusual in its duration, as it was shown to last for at least two hours. Prior synaptic stimulation also can enhance LTD induced by low-frequency stimulation in the CA1 region. Thus, a number of groups have now reported that a tetanus, which does not itself produce lasting changes in synaptic efficacy, can facilitate the subsequent induction of homosynaptic LTD (Refs 3,11,12).

To summarize the above data, prior activation of NMDA receptors, regardless of whether LTP was produced, leads to less LTP and more LTD being induced by subsequent activity (Table 1). The pharmacology of LTP facilitation remains to be clarified, although activation of metabotropic glutamate receptors might be involved (see below).

Mechanisms of metaplasticity

Most of the forms of synaptic plasticity we have discussed depend on NMDA receptor activation and a rise in intracellular Ca^{2+} ($[Ca^{2+}]_i$). Modulation of NMDA-receptor activation, or the biochemical sequelae to Ca^{2+} entry, are likely targets for metaplasticity expression. Thus, we can divide the possible sites of metaplasticity into two broad categories: (1) those processes that regulate the rise in postsynaptic $[Ca^{2+}]_i$; and (2) the downstream processes that are activated by the rise in $[Ca^{2+}]_i$.

Metaplasticity by regulation of Ca^{2+} entry

A rise in postsynaptic $[Ca^{2+}]_i$ following synaptic stimulation depends on a number of factors that might be regulated. Because most Ca^{2+} influx is voltage-dependent, one powerful site of regulation is the effectiveness of converging inhibitory synapses. It is now well established that auto-inhibition of GABA release during high-frequency stimulation promotes LTP by allowing strong depolarization and thus larger NMDA responses[22]. Longer-lasting modifications of inhibition might contribute to metaplasticity. For example, LTP of

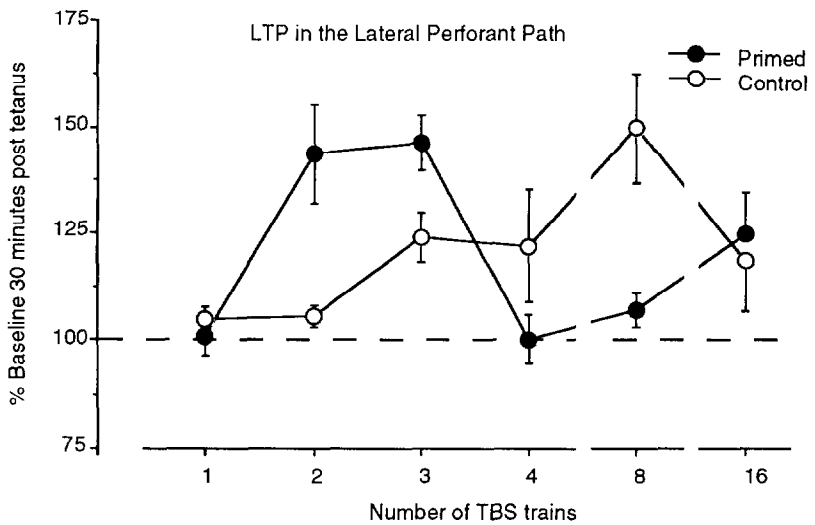

Fig. 2. ***Effect of priming stimulation on long-term potentiation (LTP) induction.*** *The lateral perforant path inputs to the dentate gyrus in pentobarbital-anaesthetized rats received priming stimulation (80 pulses at 5 Hz) followed by LTP induction 10 min later. An induction function for control paths was established, which showed a threshold for LTP at three trains of theta-burst stimulation (TBS) and a maximum level of LTP after eight trains. LTP was much less when 16 trains were delivered. When prior priming stimulation was given, the numbers of TBS trains required to produce threshold and peak levels of LTP were dramatically reduced. The reduction of LTP caused by additional trains was also shifted to the left. Priming stimulation by itself did not affect synaptic efficacy. Data points represent mean values ± SEM as a percentage of baseline values.* Figure adapted, with permission, from Ref. 10.

TABLE 1. Examples of metaplasticity

Effect of prior activity on synaptic strength	Pattern of prior activity		Effect of prior activity on synaptic plasticity	Brain area	Refs
No change	5×	100 Hz, 1 s + AP5	Increased LTP	CA1	13
	1×	ACPD 20 μM, 10 min	Increased LTP	CA1	14
	8×	5 Hz, 2 s	Increased LTP	DG	10
	6×	30 Hz, 150 ms	Decreased LTP	CA1	2
	1×	5 Hz, 3 min	Decreased LTP	CA1	5
	1×	1 Hz, 8.3–16.5 min	Decreased LTP	CA1	6,7
	8×	5 Hz, 2 s	Decreased LTP	DG	9,10
	4×	30 Hz, 330 ms	Increased LTD	CA1	3
	8×	5 Hz, 2 s	Increased LTD	CA1	11
	2×	100 Hz, 1 s	Increased LTD	CA1	12
	8×	5 Hz, 2 s	Increased LTD	DG	9
LTP	3×	100 Hz, 1 s	Decreased LTP	CA1	15
	6×	200 Hz, 75 ms	Decreased LTP	DG	15
	180×	500 Hz, 10 ms	Decreased LTP	MC	16
	180×	500 Hz, 10 ms	Increased LTD	MC	16
	4×	100 Hz, 500 ms	Increased LTD	CA1	3
	1×	100 Hz, 1 s	Increased LTD	CA1	6,17,18
	2×	100 Hz, 1 s	Increased LTD	CA1	12
	10×	100 Hz, 40 ms	Increased LTD	CA1	19,20
	80×	100 Hz, 50 ms	Increased LTD	DG	21

Both the decreased LTP and the increased LTD appear to be due to prior NMDA-receptor activation. Increased LTP might be due to prior mGlu-receptor activation. Abbreviations: AP5, aminophosphonopentanoate; DG, dentate gyrus; CA1, CA1 region of the hippocampus; MC, Mauthner cell.

inhibitory postsynaptic potentials (IPSPs) has recently been demonstrated in the visual cortex[23], and this would be expected to limit subsequent induction of LTP of excitatory synaptic transmission severely. The reported reduction of inhibition following LTP in the hippocampus should have the opposite effect[24]. Similarly, long-term regulation of K^+ channels could indirectly affect NMDA-receptor function by modulating postsynaptic excitability (for review see Ref. 25). Other putative sites of regulation include the NMDA receptors themselves, and the postsynaptic Ca^{2+} dynamics that result from activating them[26]. Stimulation of the perforant path can cause a significant increase in the synthesis of calbindin-D28K, a high affinity Ca^{2+}-binding protein, in the dentate gyrus[27]. Modelling studies indicate that even subtle activity-dependent changes in Ca^{2+} buffering, or structural changes in dendritic spines, can alter Ca^{2+} diffusion enough to be physiologically relevant[26,28,29]. A role for Ca^{2+}-buffering proteins in modulating synaptic plasticity was confirmed by the recent demonstration that transfected cultured hippocampal pyramidal cells expressing calbindin-D28K have markedly reduced post-tetanic potentiation[30]. Whether LTP and LTD are similarly affected remains to be tested. Finally, prior stimulation might modify the storage or release of $[Ca^{2+}]_i$ in response to afferent stimulation by modulating the Ca^{2+} channels or pumps in the endoplasmic reticulum.

The long-term regulation of NMDA receptors or channels deserves further comment. Already there is considerable evidence that NMDA responses can be persistently upregulated by tetanizations that also produce LTP of non-NMDA responses[31–33]. Conversely, a depression of NMDA receptor-mediated responses has also been observed following low-frequency stimulation that produces LTD (Refs 34–36). These changes in NMDA-receptor function are likely to mean that there will be alterations in the ability to induce further synaptic plasticity later on, although this has not been investigated explicitly. Lasting modifications in NMDA-receptor function are not dependent on a concurrent change in non-NMDA receptors, however, since NMDA-receptor potentiation alone has been observed following a short period of anoxia[37], and NMDA-receptor depression alone has been observed after weak tetanic stimulation[38]. Clearly, NMDA-receptor function should be a primary target for studies of metaplasticity mechanisms.

Metaplasticity by regulation of biochemical processes

There are numerous possibilities for the regulation of downstream components following an elevation in $[Ca^{2+}]_i$. Levels of $[Ca^{2+}]_i$ are believed to be translated into synaptic modifications by the actions of a network of protein kinases and phosphatases (for review see Ref. 39), and the activity or amount of these enzymes might be regulated by prior synaptic or cellular activation. For example, activation of Ca^{2+}–calmodulin kinase II (CaMK II) appears to be necessary for the establishment of LTP in the CA1 region (for review see Ref. 40). Activity-dependent regulation of functional CaMK II occurs at three levels: (1) gene expression[41–44]; (2) availability of calmodulin[45,46]; and (3) post-translational modification of the enzyme[47,48]. Metaplasticity could be explained by any or all of these modifications. Of particular relevance is the observation by Mayford *et al.*[49] that a point mutation of CaMK II that mimics the effect of autophosphorylation and makes the kinase less Ca^{2+}-dependent both raises the threshold for LTP induction and makes LTD more likely after low-frequency stimulation (see also Ref. 50).

There are good reasons to believe that metabotropic glutamate (mGlu) receptors, as well as NMDA receptors, are involved in metaplasticity phenomena, since a number of long-lasting effects of mGlu-receptor activation have recently been reported. A brief application of the

selective agonist aminocyclopentane-(1s,3R)-dicarboxylate (ACPD) can directly cause a lasting (>30 min) enhancement of pharmacologically isolated NMDA receptor-mediated excitatory postsynaptic currents (EPSCs)[51] and induce a long-lasting depression of GABA-mediated IPSPs that should indirectly enhance NMDA-receptor responses[52]. These are promising candidate mechanisms for metaplasticity since they might be relatively 'silent' when conventional recordings of field EPSPs are used, yet should profoundly influence the induction of NMDA receptor-dependent synaptic plasticity. In agreement with this prediction, there is now evidence that ACPD application can cause a persistent enhancement of LTP induction mechanisms[13,14], although the biochemical mechanisms by which this occurs remain to be elucidated. It is possible that other signalling pathways, for example cholinergic muscarinic receptor activation, might work synergistically with mGlu-receptor activation to regulate synaptic plasticity[10].

Implications of metaplasticity

The data reviewed above demonstrate that the thresholds for synaptic plasticity are not static properties of synaptic connections but, instead, vary dynamically according to the recent history of synaptic activity (that is, synapses are metaplastic). Clearly, one implication of such metaplasticity is that the degree or direction of synaptic plasticity induced by a particular pattern of conditioning stimulation cannot be predicted unless the previous stimulation history of the tissue is known. There are other implications, however, of which two will be considered.

The effect of LTP on subsequent induction of synaptic plasticity

In the examples cited above, we focused on the induction of metaplasticity in cases where it could be easily distinguished from the induction of concurrent modifications of synaptic efficacy. However, it is reasonable to assume that the two activity-dependent processes would often be induced simultaneously, as both can be triggered by NMDA receptor activation. If true, what might be some of the consequences? One obvious prediction is that LTP-inducing tetanic stimulation should inhibit further LTP induction. However, in situations where tetanizations are delivered repeatedly until no further LTP is induced, this is typically referred to as saturation of LTP. Does this phenomenon represent a saturation of LTP expression mechanisms (as conventionally believed), or is metaplasticity responsible (for example, by downregulating NMDA receptors, thereby preventing further LTP induction)? Frey *et al.*[15] recently addressed this issue by 'saturating' LTP and then looking to see if further LTP beyond the saturated level could be induced hours later. Additional LTP was found to occur eventually, possibly because the metaplasticity processes inhibiting LTP induction decayed over time[2].

Another prediction is that LTP induction should facilitate subsequent LTD induction. Indeed, in hippocampal CA1 pyramidal cells[6–9,12,17–20], as well as in the goldfish Mauthner cell[16], synaptic depression is more reliably produced following prior induction of LTP. These results might be explained by LTP raising the synaptic weights off the floor of their dynamic range, but this seems unlikely given the evidence in both systems that LTD can occur in the absence of prior LTP. We believe that the data are better accounted for by assuming that a strong tetanus, in addition to producing LTP, also induces metaplasticity which then facilitates the subsequent induction of LTD. Thus, the phenomenon of 'depotentiation', which results when low-frequency stimulation is delivered to a potentiated population of synapses, might be considered better as primed LTD.

If metaplasticity and synaptic plasticity can occur concurrently, what implications does this have for the interpretation of events occurring during LTP and LTD induction? Recall that in the dentate gyrus, LTP induction by weak stimulation was facilitated by prior priming stimulation[10]. Perhaps a similar facilitation regularly occurs during any of the long or repeated stimulus protocols that are often used to induce synaptic plasticity, such that the stimuli occurring early in a stimulation sequence prime the induction of plasticity by subsequent stimuli within the same sequence. In the case of LTD, for example, it seems entirely plausible that, during the 900 pulses (at 1–3 Hz) commonly used to induce LTD homosynaptically in the hippocampus[53], metaplasticity is set up early in the stimulus train and this facilitates LTD induction occurring later in the same train. This possibility is ripe for experimental examination since already it has been shown that significant metaplasticity can develop over the course of minutes[10].

Biochemical correlates of synaptic plasticity

One area of intense interest in the field of synaptic plasticity is the identification of biochemical and molecular correlates of LTP or LTD induction. Correlations have been made with changes in gene expression, protein synthesis, extracellular protein release, protein phosphorylation, kinase activity, receptor binding and synaptic structure. While it is understood that these studies do not causally link such changes to LTP or LTD, the connection is usually hypothesized, especially if the correlated cellular change is blocked by an agent that also blocks the synaptic plasticity, for example, a NMDA-receptor antagonist. However, we now point out that an equally likely hypothesis is that the changes under investigation pertain to metaplasticity, rather than directly to synaptic plasticity *per se*.

Concluding remarks

The data reviewed above indicate that prior synaptic activation can leave an enduring trace that affects the subsequent induction of synaptic plasticity. Many different mechanisms probably contribute to metaplasticity, as is also the case for synaptic plasticity. Indeed, there are likely to be many induction mechanisms that overlap between the two phenomena, for example NMDA-receptor activation and rises in postsynaptic $[Ca^{2+}]_i$. Any biochemical processes set in motion by neural activity could, therefore, play a role in synaptic plasticity, metaplasticity, both of them, or neither, and we are challenged to distinguish between these possibilities. On the other hand, recognition of the presence of metaplasticity might yield new interpretations of old data and provide new insights into one of the key questions in neurobiology: how is information stored in the nervous system?

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Acknowledgements
This work was partly supported by a grant from the Health Research Council of New Zealand to W.C. Abraham and by a Fogarty Senior International Fellowship to M. Bear. We thank A. Cohen, A. Heynen and R. Sayer for helpful comments on earlier versions of the manuscript.

Integrator or coincidence detector? The role of the cortical neuron revisited

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Neurons can operate in two distinct ways, depending on the duration of the interval over which they effectively summate incoming synaptic potentials. If this interval is of the order of the mean interspike interval or longer, neurons act effectively as temporal integrators and transmit temporal patterns with only low reliability. If, by contrast, the integration interval is short compared to the interspike interval, neurons act essentially as coincidence detectors, relay preferentially synchronized input, and the temporal structure of their output is a direct function of the input pattern. Recently, interest in this distinction has been revived because experimental and theoretical results suggest that synchronous firing of neurons might play an important role for information processing in the cortex. Here, we argue that coincidence detection, rather than temporal integration, might be a prevalent operation mode of cortical neurons. We base our arguments on established biophysical properties of cortical neurons and on particular features of cortical dynamics.

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ALTHOUGH OUR KNOWLEDGE about the morphological and physiological features of cortical cells has increased substantially over the past 20 years, the basic operational mode of cortical neurons has remained controversial. The traditional view, which still predominates in cortical physiology and most neural network models, considers the cortical neuron as an integrate-and-fire device. This view was advocated first by Sherrington[1] and later supported by evidence obtained from the spinal cord[2]. An alternative concept, proposed about a decade ago[3,4], suggests that neurons in the cortex operate primarily as detectors for the temporal coincidence of synaptic inputs. This proposal is motivated by the assumption that correlated activity of neurons is of crucial importance for cortical processing and that synchrony might, in particular, contribute to solving the so-called binding problem, that is, the problem of integrating distributed information into coherent representational patterns[3–8]. Such a temporal code can only be employed by the nervous system if neurons are sensitive to coincidence. Otherwise, it would be impossible to convey

0166 - 2236/96/$15.00 PII:S0166223696200086