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Micro-rewiring as a substrate for learning

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Abstract

How does the brain encode life experiences? Recent results derived from vital imaging, computational modeling, cellular physiology and systems neuroscience have pointed to local changes in synaptic connectivity as a powerful substrate, here termed micro-rewiring. To examine this hypothesis, I first review findings on micro-structural dynamics with focus on the extension and retraction of dendritic spines. Although these observations demonstrate a biological mechanism, they do not inform us of the specific changes in circuit configuration that might occur during learning. Here, computational models have made testable predictions for both the neuronal and circuit levels. Integrative approaches in the mammalian neocortex and the barn owl auditory localization pathway provide some of the first direct evidence in support of these ‘synaptic-clustering’ mechanisms. The implications of these data and the challenges for future research are discussed.

Introduction

The goal of this review is to outline an emerging theory for the neuronal basis of learning. Currently, the most referenced model focuses on synaptic weight changes occurring within a static pattern of connections. The model described here revises the second aspect, invoking as a central feature an adaptable pattern of connections produced by the ongoing formation and elimination of synapses. In non-pathological conditions, most of these structural changes occur within a small volume, just a few microns thick, surrounding the existing axo-dendritic interface. Although the spatial range is small, the power in principle of such micro-rewiring to adjust circuit function, and ultimately to store information or learned skills, is not.

Micro-structural dynamics

Recent advances in methods for imaging subcellular structures in the living brain have placed a new spotlight on the synapse. Beautiful time-lapse movies provided by several groups over the past decade reveal a previously unappreciated structural dynamism: the nascent appearance, growth and elimination of synaptic structures extending throughout life. Much of the evidence comes from visualization of dendritic spines [1,2], the principal recipients of excitatory synaptic inputs in mammalian cortex. By peering through the polished or surgically excised skulls of mice expressing fluorescent proteins in a subset of cortical neurons, researchers have shown that a small but significant proportion of dendritic spines and spine-like filopodia are motile in juveniles and young adults [3–12]. In most cases, overall dendritic morphology is remarkably stable for weeks to months, whereas, by contrast, individual spines are observed to appear or disappear within hours to days. Similar observations have been made for axonal boutons and branchlets [9,10]. The spatial extent of structural plasticity in most studies is on the order of two microns, although the occasional axonal branchlet and the dendrites of some inhibitory interneurons extend dynamically over tens of microns [11]. Both the extent and

prevalence of micro-structural change seem to be cell-type specific [12]. In total, these studies establish that micro-anatomical plasticity is robust during development and can persist well after circuits attain adult-like precision in form and function.

One important question concerns the relationship between micro-structural dynamics and the formation or elimination of synapses [13]. The latest evidence demonstrates a good correlation. Two studies of layer five pyramidal cells in the barrel cortex found that spine sprouting and retraction were associated with synapse formation and elimination as revealed by meticulous electron-microscopic reconstruction [4,8], the definitive technique for identifying synapses in fixed tissue. In cultured hippocampal slices, manipulation of the actin-binding protein Nr1I caused an increase in both spine motility and the number of synapses formed per length of dendrite [14]. In cultured cortical neurons, knockdown of EphB2 receptors suppressed both filopodial extension and the proliferation of synaptic punctae that normally occurs during epochs of high motility [15]. Collectively, these observations support the notion that microstructural dynamics serve a synaptogenic function and, in addition, lay a path for unraveling the molecular bases of spine motility and synaptogenesis.

Complementary studies have used physiological approaches to monitor the making and breaking of synapses. In one experiment, neurons in live slice were patched, sealed and re-patched after 12 h of stimulation with glutamate [16]. Entire cohorts of functional contacts between neighboring neurons were switched on and off over this time. Pharmacological manipulations seemed to rule out potentiation of silent synapses as an explanation for the appearance of the new input. Although definitive micro-anatomical evidence is lacking from this paradigm, the results are most readily explained by activity-driven formation and elimination of functional synapses.

Box 1

Take-home messages

- i. Dynamic extensions of dendritic filopodia and axonal branchlets, in the order of a few microns, have been observed in juvenile and adult brains. These dynamics probably serve to sample the local environment for new synaptic partners.
- ii. Of all the potential changes in microcircuit configuration that could be achieved through targeted synapse formation and elimination, one broadly applicable principle is clustering of co-active inputs. This prediction hinges on the behavior of dendrites as non-linear integrators.
- iii. Direct empirical evidence in support of the synaptic-clustering model has recently emerged from anatomical studies in the owl midbrain and physiological studies in the mammalian cortex.
- iv. The synaptic dynamics that underlie changes in clustering are unknown. I present two models that make distinct, testable predictions. A complete understanding of these phenomena will probably depend on interaction between researchers interested in micro-rewiring and those already investigating the molecular mechanisms of synapse assembly and disassembly.

What are the implications of these observations for the mechanisms of learning? Filopodial and branchlet extension are hypothesized to create new connections that are tested for adaptive value via a 'Hebbian' process and consequently stabilized or eliminated to yield a new, optimized wiring diagram (Box 1). The parameter space of available wiring diagrams is likely to be enormous [17]. Geometric analysis of anatomically reconstructed cortical neurons indicates that nearly all neighboring neurons have the potential to be or become connected

[18,19]. Although the proportion of pairs actually connected remains unknown, the wiring flexibility illustrated by this analysis begs the question of whether certain connection motifs are exploited as substrates for learning.

Location matters

One way micro-rewiring could boost learning capacity is through the dendritic re-addressing of synapses according to their information content. If individual dendrites perform non-linear operations, then orchestrated shifts in synapse location are expected to significantly enhance pattern detection and ultimately represent a reservoir for information storage [20,21].

The bulk of computational and experimental evidence indicates that summation between dendritic branches is nearly linear. By contrast, the crucial issue of whether excitatory postsynaptic potential (EPSP) summation within branches is linear or non-linear has not been definitely resolved. Computational models using reconstructed cortical or hippocampal pyramidal cells predict that individual dendrites can act as non-linear integrators owing to the presence of active conductances, including voltage-gated sodium and calcium channels and *N*-methyl-D-aspartic acid (NMDA) receptors [22]. Specifically, co-activation of synapses located within ~40 microns of one another (on the same branch) produces a much stronger dendritic response than expected from the sum of individual activations. Empirical studies focusing on within-branch summation, probed by using small numbers of optically or synaptically evoked inputs, have found integration modes that range from mostly linear in CA1 pyramidal cells [23,24] or cerebellar Purkinje cells [25] to strikingly non-linear in other cortical neurons [26]. One intriguing possibility is that some dendrites actively switch between different integration modes depending on the spatiotemporal input regimen or the intrinsic state of the neuron [27].

An alternative form of non-linear processing was recently found to occur in the dendrites of CA1 pyramidal neurons [28]. Using rapid multi-site glutamate uncaging to synchronously activate a larger number of spines (5–20), it was found that the effective propagation of dendritic action potentials to the cell body was highly variable from branch to branch, supralinear above a threshold [29] and, moreover, modifiable with experience. Specifically, repeated activation of cohorts of synapses located on the same branch resulted in NMDA-dependent downregulation of Kv4.2 potassium channels, which normally function to depress excitability. In response, propagation to the soma was enhanced for the stimulated branch only. This ‘branch-strength potentiation’ represents a novel form of non-linear communication between synaptic cohorts and the soma [28]. In addition, this study highlights the utility of probing dendritic-integration rules using large numbers of synaptic activations, which better resemble *in vivo* stimulus patterns than do paradigms that employ small numbers of activations.

Given this evidence for non-linear summation in certain cell types and conditions, what are the implications for learning? This question has been addressed by an elegant series of computational studies that analyzed the processing power of biophysically realistic model neurons receiving moldable patterns of input [21]. With 1000 or more synapses scattered across their dendritic fields, the number of input patterns that could reach each cell was vast. The job of the cell was to learn to detect recurring patterns and respond with action potentials. The model predicts that, as a result of learning, co-active synapses become clustered together onto short lengths of dendrite (Figure 1). This synaptic clustering enhances the postsynaptic response elicited by those inputs, even without a change in their number or strength. Forging an efficient pattern detector without increasing the number of synapses is attractive from a homeostatic standpoint, because it does not challenge the continually learning brain with synaptic overcrowding. Moreover, neural network models indicate that the storage capacity of circuits that employ dynamic clustering in combination with synaptic potentiation and

depression is predicted to be much larger than the storage capacity of circuits molded solely by adjustments in synaptic weight [21].

The remainder of this review focuses on this synaptic-clustering model (Box 1). It should be noted, however, that the concept of micro-rewiring is broad and is likely to involve other cellular and network properties that collectively contribute to learning, pattern detection and information storage. In brief, these factors include the electrotonic properties of dendrites [30], gradients of learning rules for synaptic weight change [31,32], the existence of functional units defined by biochemical integration within dendrites [33], selective adjustments in the balance between excitation and inhibition [34,35] and the opportunity to create entirely novel input patterns regardless of integration mode.

Anatomical evidence for synaptic clustering

To directly test whether learning can drive changes in synaptic clustering, my research group has analyzed microcircuit configurations in the barn owl auditory localization pathway [36]. This system presents unique advantages because the functional plasticity occurs within the context of a topographic map and, therefore, the co-activation histories of labeled axons and dendrites can be inferred from their relative locations within fixed tissue. We focused on the monosynaptic connection between the lateral shell of the central nucleus of the inferior colliculus (ICCl) and external nucleus of the inferior colliculus (ICX) (Figure 2). To label the presynaptic inputs, focal injections of fluorescent anterograde tracer, micro-ruby or texas red dextran amine, were placed at defined map locations within ICCIs. Neighboring neurons in ICCIs display very similar tuning for auditory spatial cues [37–39] and, thus, because the injection sites were well contained to a few (~5) neighboring cell bodies, the neurons labeled by this method must have been co-active during the lifetime of the owl. The tracer diffused intracellularly to fill the distal tips of axons, revealing their synaptic contacts onto dendrites of neurons located in the ICX. Immunolabeling for calcium/calmodulin-dependent protein kinase II (CaMKII) served as an effective ‘fluorescent golgi stain’ to visualize these postsynaptic dendrites [40].

The exploitable trick in this system is that the labeled, co-active axons spread over a large anatomical range, contacting dendrites at map locations where they drive strong responses and locations where they drive weaker responses (Figure 2a). This disconnect between macro-anatomical configuration and functional circuit strength is particularly dramatic in owls that have adapted to life wearing prismatic spectacles [41]. Prisms optically displace the visual field, resulting in misalignment between the auditory space map and its instructive visual inputs. With time, this conflict is resolved through the experience-driven strengthening of postsynaptic responses at adaptive map locations and the weakening of postsynaptic responses at normal map locations. The obvious question is whether the extent of synaptic clustering occurring in these zones mirrors the functional adjustments in micro-circuit output. It does (Figure 2).

Using inter-contact distance (ICD) as a metric for clustering, we found two distinct learning-driven effects. The first was an increase in clustering in the adaptive zone. As shown in Figure 2b(i), shorter-range ICDs (<10–20 μ m) were prevalent in both normal juvenile (before learning) and prism-adapted owls (after learning), but longer-range ICDs, >20 μ m, were conspicuously absent from the adaptive zone of prism-adapted owls; spatially isolated contacts had been eliminated. The second was a decrease in clustering in the normal zone, in which longer-range ICDs were more prevalent after learning, as shown in Figure 2b(ii). Thus, synaptic clustering was adjusted bidirectionally during prism learning and the reconfigured patterns matched the functional strengths expressed within the behaviorally relevant microcircuits.

These data provide the first direct micro-anatomical evidence in support of the synaptic-clustering hypothesis [20–22,42–44].

Our experiments focused exclusively on clustering patterns before and after learning. What happens in between? The following two sections address related aspects of this question. First, how are clusters of co-active synapses established on the dendrite? Second, how do individual synapses that comprise the cluster become stabilized?

How do co-active clusters form?

There is no direct empirical evidence addressing this important question, although clues are evident in the large literature on the molecular mechanisms of synaptic assembly. With the goal of stimulating cross-discipline discussion, I present two models to account for the learning-driven appearance of co-active synaptic clusters. It should be straightforward to extend these principles to models of cluster disassembly, not outlined here owing to space constraints.

The first model is that new synapses representing co-active sources form at random locations along the dendrite and then are subject to experience-dependent selection (Figure 3a). One attractive feature of this Hebbian model is its simplicity, relying on undirected synaptic growth. In the initial phase of learning, a new synapse, by chance, locates as a dendritic neighbor to a co-active input. The synapses within this effective cohort would be selectively tagged or stabilized, preventing or dissuading their elimination by a constitutive process that indiscriminately targeted all non-tagged or non-stabilized synapses. By contrast, synapses that did not locate within an effective cohort would eventually be removed. In total, these processes would sort through and test scores of micro-wirings, reinforcing configurations that work and gradually disposing of ones that don't, all without changing the number or density of synapses (Box 1).

The alternative model is that new synapses are placed precisely from the onset. This 'directed' model requires some form of transneuronal communication before synapse formation. To be effective at recruiting only co-active inputs, these signals must preserve the temporal response pattern at both the existing synapse(s) and the recruited source(s). This could be accomplished by the release of a diffusible extracellular messenger with an effective spatial range in the order of microns, for example a neurotransmitter or neuromodulator, to avoid convolution with messages generated by neighboring dendrites, or through membrane-bound ligand–receptor interactions that communicate the time-course of membrane depolarization from one cell to the other. Candidates for the latter include gap junctions, whose appearance precedes a wave of synapse formation in the developing visual cortex [45], or possibly transient receptor potential channels, whose activation triggers are poorly understood [46]. In either case, detection of coincident action potentials in the post-synaptic neuron and soon-to-be recruited input would lead to synapse assembly at the site of contact or close apposition [47].

How are co-active clusters stabilized?

Once a cluster of nascent synapses representing co-active input is established, the input pattern needs to be consolidated. This requires the potentiation and stabilization (resistance to elimination) of those inputs. One possible complication, however, is the tendency of newly formed synapses to be functionally weak. Their EPSPs are mediated predominantly by NMDA receptors, which, absent modest to strong extrinsic depolarization of the postsynaptic dendrite, do not pass current. Therefore, even a cluster of new synapses might prove ineffective in driving the postsynaptic neuron. This limitation could be overcome if neighboring co-active synapses interacted biochemically within the dendrite to promote each other's strengthening.

Demonstration of just that phenomenon was recently provided by an impressive series of experiments on the dynamics of synaptic plasticity [48]. Focusing on the dendrites of hippocampal pyramidal neurons in the mouse, it was asked whether long-term-potential (LTP) induction at a single synapse influences the threshold for LTP at neighboring synapses. Individual synapses were stimulated by localized photo-uncaging of the transmitter glutamate, a procedure that effectively activates receptors on just one spine. Pairing uncaging with strong depolarization imposed through a patch electrode produced synapse-specific LTP, manifest in the potentiation of EPSCs recorded at the soma and physical enlargement of the stimulated spine. By contrast, a similar but less vigorous stimulation protocol produced no LTP or spine enlargement when applied to naïve dendrites. These synapse-specific ‘superthreshold’ and ‘subthreshold’ induction protocols provided tools to probe for spreading effects.

The key result is shown in Figure 4. When the subthreshold protocol was applied to synapses located near (no further than $\sim 10\ \mu\text{m}$) one that had been recently potentiated by superthreshold induction, the subthreshold protocol elicited LTP. Using spine enlargement as a proxy for synaptic strengthening, it was shown that this crosstalk in plasticity between neighboring synapses also occurred in response to more physiological induction protocols, uncaging in unperturbed neurons or synaptic stimulation. Moreover, the spreading effect lengthened the temporal integration window for LTP induction to at least 35 ms, indicating that neighboring synapses were being given a better-than-usual chance to join the effective cohort. Finally, a related study found that LTP induction triggered Ca-dependent activation of the small GTPase Ras, which then spread by diffusion to invade nearby spines. Indeed, Ras signaling was required to lower the threshold for LTP at neighboring synapses [49]. In total, these observations reveal a mechanism that could be used during normal behavioral episodes to promote the strengthening, and possible stabilization, of newly formed co-active synaptic clusters.

Both the physiological [48] and the anatomical evidence [36] provided indicate an effective synapse cluster size of $\sim 10\text{--}20\ \mu\text{m}$. This is somewhat smaller than the maximum distance over which strong supralinear summation is predicted to occur, $\sim 40\ \mu\text{m}$ [21,22,26]. One possible explanation for this discrepancy is that the dendrites of different cell types express complements of ion channels that confer customized spatial windows for non-linear integration. A non-exclusive possibility is that maximizing the functional interactions within a consolidated synaptic cluster requires, in addition to (or instead of) electrical summation, biochemical integration operating over a more limited spatial range. Integration of synaptically induced Ca transients is a prime candidate for the latter; however, it is important to note that the mechanisms of functional integration within mature synaptic clusters and those necessary for the induction or stabilization of nascent clusters could represent distinct phenomena.

Future challenges

There are several. Technically, there is need for continued development of methods to effectively visualize micro-wiring patterns involving thousands of synapses distributed across millions of cubic microns of tissue. One current approach is high-resolution confocal microscopy or two-photon imaging. Although definitive synapse identification is not possible at the light level, the co-application of morphological, physiological and molecular criteria might present an acceptable trade off between false positives (contacts that aren't synapses) and high-throughput capacity (the advantage of this technique) [36,40,50–52]. Two promising new methods include serial block-face electron microscopy [53] and array tomography [54], which might provide both ideal resolution and the required throughput, especially in conjunction with new segmentation methods for automated image analysis [55].

Towards what biological questions would these techniques be applied? One immediate need is to determine whether the clustering changes observed in the owl auditory system represent

an isolated finding or the tip of the tail of the tiger. The mapping of topographically organized mammalian microcircuits, such as the retinogeniculate and geniculocortical pathways after manipulations of visual input or the intracortical connections of the somatosensory system after whisker trimming, should be invaluable in achieving this goal. Another need is to determine whether experience-dependent changes in micro-wiring extend to diverse circuit elements, that is, morphologically or molecularly defined subclasses of excitatory, inhibitory and modulatory neurons. Within the vast architecture that would be revealed by such experiments, several additional aspects of the clustering model could be examined. Do non-active synapses converge onto the same dendritic branch and, if so, do they segregate? Where dynamic clustering does occur, what are the time-lapse dynamics? One crucial issue amenable to such an approach concerns the differential predictions of the Hebbian versus directed models outlined in Figure 3. Finally, it would be of great interest to determine whether the adult brain, which usually exhibits a lower rate of micro-structural dynamics, also employs micro-rewiring as a substrate for learning.

A second challenge is to understand better the input–output operations mediated by dendrites. For example, does optimized input clustering on dendrites actually forge a superior pattern detector? Recent development of a photostimulation device capable of delivering up to 20 000 uncaging events per second, and thereby producing complex and physiologically relevant patterns of synaptic input, should boost this effort [56].

Much work thus far has relied on gross manipulations of activity as blunt tools to induce change. A third challenge is to ask how, or whether, naturalistic patterns of experience produce similar affects. To this end, model systems with strong neuroethological importance should prove instructive in illuminating principles that apply across brain regions and across species.

The long-term challenges are to identify the types of sensory processes and memory functions in humans that depend on micro-rewiring. Do disruptions in this process contribute to disabilities? If so, development of pharmacological and behavioral methods targeted specifically towards triggering or optimizing micro-rewiring might pave the way towards amelioration. Finally, if we understood how learning occurs in the brain, the principles could be applied to the design of artificial networks, with potentially far-reaching consequences.

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Figure 1.

The synaptic-clustering model. **(a)** A postsynaptic neuron with three dendritic branches and no synaptic input. **(b)** The same neuron loaded with a full complement of synapses representing three independent input sources (red, dark blue and aqua circles). Each input source consists of synapses arising from either the same axon or from different axons (different presynaptic neurons) with very similar response profiles. The dendritic addresses of the inputs are dispersed randomly across the dendritic field. For clarity, axons are not depicted in this diagram or in other figures. According to the model, activation of each input source would produce EPSPs that sum linearly, producing a weak output in terms of the number of action potentials generated at the soma. **(c)** The same neuron after changes in microcircuit connectivity triggered by behaviorally driven activation of the input sources. During this learning period, ongoing synapse formation and elimination provided a mechanism to change the dendritic addresses of the inputs. The top dendrite gained red synapses and lost blue and aqua ones. These gains and losses were offset in number by changes occurring on the other dendritic branches, which became dominated by blue and aqua, respectively. Re-addressing occurs predominantly by the making and breaking of synapses, not the sliding of pre-existing ones along the dendrite. Regardless of the structural mechanics, clusters of co-active synapses have appeared along short stretches of dendrite. In the new microcircuit configuration, EPSPs driven by activation of each input source are predicted to interact supralinearly and, thus, elicit a strong postsynaptic response. The neuron has effectively stored information about three separate spatiotemporal input patterns. Modified, with permission, from [Ref. 21].

Figure 2.

Learning-driven clustering of axo-dendritic contacts in the barn owl auditory localization pathway. **(a)** Read this panel from bottom up. Data for normal juveniles (before learning) are depicted in (i) and for prism-adapted owls (after learning) in (ii). Tracer injections were placed in the ICCLs (lateral shells of the central nucleus of the inferior colliculus) at map locations representing $\sim 10^\circ$ contralateral space (i, ipsilateral; c, contralateral). In normal juveniles, the labeled co-active axons (red lines) spread over ~ 2 mm in ICX (external nucleus of the inferior colliculus), where they synapse onto dendrites strongly expressing CaMKII (grey neurons). Axo-dendritic contacts between ICCLs axons and CaMKII+ dendrites (red dots on grey neurons) were identified in high-resolution confocal images on the basis of strict morphological and molecular criteria [36]. These contacts express many hallmarks of true synapses. To quantify synaptic clustering, we measured the distance from one contact to the next on individual branches of dendrite. The results from this quantitative analysis are illustrated schematically by the clustering patterns drawn onto the CaMKII+ neurons. In normal juveniles, inter-contact distances (ICDs) were, on average, smaller near the central aspect of the axonal arbor (normal zone; region 2) than on the flanks (adaptive zone; region 1), indicating greater

synapse clustering in the normal zone. These clustering patterns mirrored the functional circuit strengths measured *in vivo* by electrophysiological mapping (stylized tuning curves at the top of the figure). By contrast, in prism-adapted owls, clustering was greatest on the adaptive flank (region 3), which is determined by the direction of prismatic displacement (red arrow at top of figure; Vrf, visual receptive field), and now weaker in the normal zone (region 4). Again, the microcircuit configuration mirrored the functional circuit strengths. It should be pointed out that the experimental design described in [Ref. 36] is a subtle variant of the hypothesis in [Ref. 21], as it focuses on the clustering of inputs whose adaptive value is determined by an additional, extrinsic signal acting on the postsynaptic neuron (called the instructive signal [41]), and not solely by co-activity. **(b)**, Frequency distributions of ICDs for the adaptive and normal zones of normal juveniles (regions 1 and 2) and prism-adapted owls (regions 3 and 4). Data were normalized to peak occurrence. Data in (i) demonstrate that learning-driven de-clustering of contacts in the normal zone occurred predominantly by the appearance of longer range ICDs. Data in (ii) demonstrate that the learning-driven clustering of contacts in the adaptive zone occurred predominantly by the elimination of longer range ICDs. Modified, with permission, from [Ref. 36].

Figure 3.

Two models for the experience-dependent clustering of co-active synapses. Both models begin with a single branch of dendrite, 100 μm in length, contacted by three non-co-active synapses (red, dark blue and aqua circles). Thin arrows depict events involved with synaptogenesis. Solid thick arrows depict the tagging and/or stabilization of co-active synapses. Dashed arrows depict the random elimination of all non-tagged and/or non-stabilized synapses. **(a)** The Hebbian model is based on random placement of new synapses, depicted by the addition of a red synapse to either of two dendritic locations. When located away from the pre-existing red synapse (>20 μm), as shown on the upper branch, the EPSPs are subject to linear integration and, thus, form an ineffective cohort. None of the four synapses now occupying the branch have established their functional importance nor achieved a competitive advantage for stabilization. They are equally liable to a constitutive elimination process, necessary to both prevent overcrowding and ensure that a large range of micro-wirings is performance tested. By contrast, when the new synapses is, by chance, located near (<20 μm) an existing co-active input, as shown on the lower branch, supralinear interactions drive the postsynaptic cell to threshold, rewarding the recently activated synapses with a synaptic tag or stabilization factor

(white dots on red synapses). They are now resistant to elimination. The cluster is preserved for the lifetime of the tag and/or stabilization factor, which could be renewed as long as the cluster continues to effectively fire the postsynaptic cell. An alternative molecular scheme is that, upon creation, all synapses are marked for elimination, and synaptic tagging and/or stabilization removes this mark. **(b)** The directed model is based on the precise placement of new synapses. This requires the production of a transneuronal signal, depicted by brackets surrounding the dendrite, by the existing synaptic contact. The spatial range and lifetime of this signal must be short, so that it does not recruit non-co-active axons. If a co-active axonal branchlet or bouton appears within this spatiotemporal window, a synapse is assembled. The remaining events are as described in the Hebbian model.

Figure 4.

Locally dynamic synaptic learning rules in pyramidal neuron dendrites. **(a)** Diagram of a postsynaptic neuron before induction of synaptic plasticity. Five synapses (1–5) distributed along the apical dendrite are depicted with small red circles. **(b)** Independent activation of any one of these synapses using the subthreshold LTP induction protocol (dashed lines) does not lead to potentiation. **(c)** Independent activation of synapse 3 using the superthreshold protocol does lead to synapse-specific potentiation (larger red circle with white core). **(d)** For the conditioned branch of dendrite, subthreshold induction does result in potentiation for synapses close to (2 and 4) but not far away from (1 and 5) the seminal potentiated synapse 3. The data indicate that synaptic clusters produced by this spreading effect would be 10–20 μm in total. The locally dynamic learning rule revealed by these experiments resembles, in certain ways, a phenomenon known as synaptic tagging [57] but is distinct in requiring the weak stimulus to follow the strong one and not requiring translation of new proteins. Thus, the current results do not provide support for (nor do they disprove) a previously described model of the molecular

mechanisms of underlying clustered plasticity [43]. Modified, with permission, from [Ref. 48].