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Stability of the fittest: organizing learning through retroaxonal signals

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Classically, neurons communicate by anterograde conduction of action potentials. However, information can also pass backward along axons, a process that is essential during the development of the nervous system. Here we propose a role for such 'retroaxonal' signals in adult learning. We hypothesize that strengthening of a neuron's output synapses stabilizes recent changes in the same neuron's inputs. During learning, the input synapses of many neurons undergo transient changes, resulting in altered spiking activity. If this in turn promotes strengthening of output synapses, the recent synaptic changes will be stabilized; otherwise they will decay. A representation of sensory stimuli therefore evolves that is tailored to the demands of behavioral tasks. We describe a candidate molecular mechanism for this process involving the activation of CREB by retrograde neurotrophin signals.

Introduction

The function of the brain is to transform sensory input into muscle contractions and gland secretions to promote the survival and reproduction of an animal. Most neurons, however, neither directly transduce sensory input nor directly connect to effector cells. These neurons therefore perform intermediate steps in the computation of appropriate behaviors. The firing of neurons in the central nervous system can represent an incredible diversity of information, from simple features of visual scenes [1], to places and people [2,3] and abstract rules [4]. These representations are capable of rapid plasticity [5,6], but can also remain stable for long periods of time [7,8]. Neural representations are adapted not only to the structure of sensory inputs but also to the demands of behavioral tasks [9,10], often appearing uncannily like intermediate steps of a transformation from sensory input to motor output [11].

The mechanisms by which neural representations are formed are currently unclear. One principle likely to play an important role is Hebb's rule [12], whereby a synapse which repeatedly takes part in firing the postsynaptic cell will be strengthened. Substantial evidence now suggests that this principle does indeed operate in the nervous system [13]. The idea that Hebbian plasticity plays a role in learning is also supported by the fact that artificial neural networks based on Hebbian principles are capable of performing information-processing tasks [14]. However, in the 50 years since the first such machines were built, the limitations of computational networks constructed from purely Hebbian principles have also become apparent [15]. In particular, construction of purely Hebbian networks that produce the complex internal representations needed for real-world information-processing tasks has proved challenging.

Intriguingly, the neural network algorithm that has been most successful in real-world applications uses mechanisms beyond Hebb's rule to generate internal representations. This algorithm is known as 'error backpropagation' or 'backprop' [16]. In the backprop net, the firing of simulated neurons is determined by classical anterograde transmission. However, synaptic plasticity in this network requires a 'training signal' to flow backward along the same connections, so that each neuron integrates a training signal from precisely those cells to which it sends axons. When an input pattern is presented to the network, each neuron integrates the retrograde training signals arriving from its synaptic targets, and adjusts the strengths of its input synapses based on their correlation with this integrated training signal. In the backprop algorithm, feedback from target cells is therefore *instructive*, meaning that it tells each cell whether to increase or decrease its response to its current pattern of input. This instructive signal allows each simulated neuron to generate a representation that is specifically tailored to the requirements of its target cells, and thus to the production of appropriate network outputs.

Although the backprop algorithm rapidly saw success in real-world applications, it was not originally considered as a serious model for neuronal plasticity in the brain because of the requirement for information to pass backward along axons – a process we shall refer to as *retroaxonal signaling*. Some remarkable recent experiments by Poo and colleagues, however, have shown that retroaxonal signals can indeed exert control over a cell's input synapses [17–19]. This fact is of great significance for theories of neural information processing, because it indicates that in the brain, as in the backprop algorithm, retroaxonal signals might be able to organize the construction of the internal representations necessary for complex behaviors.

So does this mean the backprop algorithm itself could be implemented by the brain, after all? The answer still appears to be no, because retroaxonal signaling in the brain is too slow. In the backprop algorithm, weight changes are based on the instantaneous correlation of

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presynaptic activity and the retroaxonal training signal, requiring that the training signal arrives while the input pattern is still being presented. Given that synaptic timescales are typically of the order ~10 ms, whereas the timescales of known forms of retroaxonal signaling are orders of magnitude slower, computation of instantaneous correlations seems impossible. The aim of this article is to propose a framework in which retroaxonal communication occurring on realistic timescales could guide the formation of behaviorally adapted representations.

This framework is based on the hypothesis that *strengthening of a neuron's output synapses stabilizes recent changes in the same neuron's inputs*. In this scenario, retrograde signals are not instructive but selective: during learning, changes in a neuron's input synapses lead to changes in its spiking pattern, which may or may not lead in turn to changes in output synapses. If the new spiking pattern promotes formation or strengthening of outputs, the recent changes to the neuron's input synapses are retained; if not, the changes decay (Figure 1). This process would lead to a gradual evolution of internal representations suited for the needs of target cells, and thus for performance of required behaviors.

There are two components to this hypothesis. First, a signal encoding changes in the strength of a neuron's output synapses must be retroaxonally propagated to the soma. Second, this signal must control the consolidation of recent changes in the neuron's input synapses. In this article, we review recent research on the mechanisms of retroaxonal signaling and synaptic consolidation, and describe how the overlap of the molecular pathways involved in these processes supports a possible interaction. We discuss the computational implications of our hypothesis, and review recent electrophysiological recordings during learning tasks in this context. The evidence we will present is circumstantial; however, the convergence of multiple lines of evidence, from molecular mechanisms to studies in behaving animals, suggests at least that this hypothesis deserves serious experimental investigation.

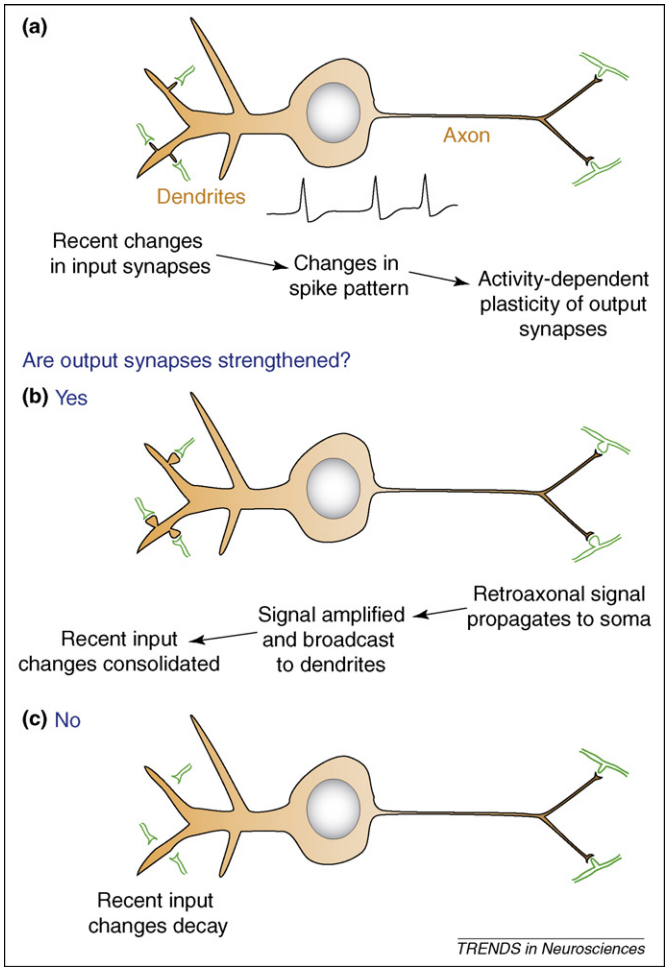

Figure 1. The hypothesis: strengthening of a neuron's output synapses stabilizes recent changes in the same neuron's inputs. **(a)** Changes in a neuron's input synapses lead to an alteration in its spiking pattern. This may or may not in turn lead to plasticity of output synapses. **(b)** If the neuron's output synapses are strengthened, this initiates a retroaxonal signal that propagates via the soma to the dendrites, and causes consolidation of the recent changes in inputs; changes in the neuron's spike pattern therefore become permanent. **(c)** If output synapses are not strengthened, however, the retroaxonal signal is not received, the recently changed input synapses decay to their prior state and the neuron reverts to its original spiking pattern. In this figure, synaptic strengths are illustrated by spine size.

Neuronal communication beyond the action potential

In the classical form of neural communication, an action potential is conducted rapidly along an axon, triggering neurotransmitter release from presynaptic terminals. Action potentials are, however, just one of many ways that neurons can communicate with each other. Neurons release and receive many signaling molecules other than classical neurotransmitters, and the release of these substances can be controlled by intracellular events other than action potentials [20–22]. Although classical neural signaling is unidirectional from the presynaptic to postsynaptic cell, other signals propagate in the opposite direction [23–25]. We will use the words *retrosynaptic* to describe signaling across the synaptic cleft from the postsynaptic to presynaptic cell, and *retroaxonal* for communication along an axon from a presynaptic terminal to the soma of the presynaptic cell.

A large number of molecules are capable of carrying retrosynaptic signals (Box 1). The release of many retrosynaptic signals occurs together with changes in synaptic strength. Thus, although the precise involvement of individual retrosynaptic molecules in expression of the various forms of synaptic plasticity is still a matter of research, the combination of retrosynaptic messages received at an axon terminal is likely to provide detailed information about changes in synaptic strength. We next consider the mechanisms by which this information could be conveyed retroaxonally to the presynaptic neuron.

Retroaxonal signals in nervous system development

Evidence that neurons are capable of carrying retroaxonal signals first came from experiments showing that the survival of developing spinal neurons depends on signals received from their target muscles [26,27]. Later research has shown that the survival of many other cell types is influenced by retroaxonal signals [28,29]. Several molecules collectively known as *neurotrophic factors* are released by target cells, which serve to attract axons and promote synapse formation. Uptake of neurotrophic factors initiates a retroaxonal signal which promotes the

Box 1. Retrograde signal carriers

Intensive research in the last two decades has identified a large and growing list of molecules capable of carrying retrosynaptic messages. The motivation for most of this research has been their potential role in plasticity at the synapse of release, rather than their ability to induce retroaxonal signals; for this reason, more is known about their local effects than their effects on the presynaptic soma. Although there is much still to be learned about how individual molecules are involved in expression of the many forms of synaptic plasticity, it is clear that multiple retrosynaptic signals are differentially activated when synaptic changes are induced. Together, these signals can therefore form a 'population code' providing detailed information about changes in synaptic strength to the axon terminal that could then be relayed to the presynaptic cell's nucleus. Potential carriers of retrosynaptic signals include:

Neurotrophins
Neurotrophins are a family of secreted proteins originally discovered as initiators of retroaxonal signals that control the survival of developing neurons. Neurotrophins also play an important role in adult synaptic plasticity [73]. Neurotrophin secretion is increased by LTP and reduced by LTD [52–54], and is important for formation of L-LTP [50,51].

Other secreted proteins
An increasing number of proteins originally known for their roles in embryonic development and axon guidance (such as members of the Wnt, TGFβ and semaphorin families) are known to be involved in synapse formation, synaptic plasticity and the initiation of retroaxonal signals [32,33,40,74].

Cell-adhesion molecules
Several proteins present in pre- and postsynaptic membranes make physical contact across the synaptic cleft. In addition to providing mechanical adhesion, these molecules can transmit bidirectional signals that are important in the formation and plasticity of synaptic connections [75].

Lipids
Neuronally released lipids such as endocannabinoids and arachidonic acid metabolites are believed to play a role in synaptic plasticity, particularly certain forms of synaptic depression [76,77].

Gasses
Small molecules such as NO and $O_2^{\bullet}$ that are synthesized during induction of LTP are able to diffuse rapidly across the synaptic cleft, where they might participate in LTP expression [78,79].

survival and growth of the innervating neuron, whereas neurons receiving insufficient neurotrophic factors might not live to adulthood. Limited secretion of neurotrophic factors by target cells can thus lead to competition among potential innervators, with the winners – those forming sufficient output connections – surviving, and the losers dying [30,31]. This has a certain logic to it: a neuron with no outputs serves no function, and so its death can only benefit the host organism.

Retroaxonal signals control many developmental processes other than cell survival [32,33]. Importantly, several recent studies show that retroaxonal signals can indeed control the plasticity of input synapses. In developing *Xenopus* embryos, application of BDNF (brain-derived neurotrophic factor) to the tectum, but not the retina, causes increased branching of dendritic arbors of retinal ganglion cells [34]. Furthermore, application of BDNF to the tectum increases both dendritic AMPA conductances and light-evoked synaptic responses in retinal ganglion cells, within a timescale of ~20 min [17]. Further evidence for retroaxonal effects on input synapses comes from cultured hippocampal cells. Induction of long-term potentiation (LTP) or long-term depression (LTD) in a neuron's output synapses can cause corresponding changes in strength of the same neuron's inputs, even if these input synapses were not themselves experimentally activated [18,19].

Mechanisms of retroaxonal signaling

The mechanisms of retroaxonal communication have been best studied for the case of signals induced by neurotrophins (NTs). The most prominent model suggests that retroaxonal signals are conveyed by physical transport of a 'signaling endosome' – a small vesicle that carries the NT molecule, the activated receptor and other associated signaling molecules [35,36]. When this retroaxonal signal arrives at the soma it initiates several cascades, including activation of the transcription factor CREB (cyclic AMP response element binding protein), which is critical for promoting neuronal survival [37–39].

Neurotrophins are not the only molecules capable of initiating retroaxonal signals. However, studies of most systems again suggest the physical transport of some kind of signal carrier [32,33,40–45]. It has been suggested that faster mechanisms, such as regenerative calcium or phosphorylation waves, might operate in parallel with physical transport [46,47]. Even these mechanisms, however, could not carry information at the millisecond timescales necessary for the instructive signals that would be required by the backprop algorithm. For the scenario we propose here, in which retroaxonal signals play a selective rather than instructive role, rapid signaling is not required.

The control of synaptic stability

The second component of our hypothesis is a process by which retroaxonal signals could promote stabilization of recent modifications to input synapses. The fact that transient synaptic modifications can be consolidated by a later stabilizing signal has been shown in a paradigm called 'synaptic tagging' [48]. In hippocampal slices, weak tetanic stimulation of Schaffer collaterals produces a transient potentiation known as 'early LTP' (E-LTP) that decays with a timescale of ~1 h. Stronger tetani induce 'late LTP' (L-LTP) that lasts as long as can be measured. However, E-LTP can be transformed into L-LTP if a second input is strongly stimulated within about an hour of the weak stimulation. The weak stimulus is said to set a 'synaptic tag' that can be consolidated by the later strong stimulus. L-LTP requires gene expression; although the genes involved have not yet been fully identified, it appears that their expression can be triggered by CREB activation [49], and that BDNF plays a role in LTP stabilization [50,51].

A candidate molecular mechanism for retroaxonal stabilization

We have seen that plasticity of a neuron's output synapses can cause a retrosynaptic signal to be transduced at its axon terminals; that the axon terminals can send retroaxonal signals to the soma, causing changes in gene

expression; and that changes in gene expression can consolidate otherwise transient changes in input synapses. Furthermore, although retroaxonal signals are unlikely to travel fast enough for neural implementation of the backprop algorithm, they can easily propagate within the ~1 h time window for consolidation of synaptic tags. Our hypothesis, that strengthening of a neuron's output synapses stabilizes recent changes in its inputs, is thus well within the known capabilities of neurons.

Although many molecules could potentially underlie this process, neurotrophins are particularly attractive candidates. In several systems, the conditions leading to NT release seem to mirror those causing synaptic plasticity, with LTP-inducing stimulation patterns causing increased release of NTs but LTD-inducing stimuli causing decreased release [52–54]. Uptake of NTs at axon terminals can initiate retroaxonal signals leading to CREB activation in the nucleus [37–39], and CREB activation can cause consolidation of recent transient changes in input synapses [49]. *In vivo*, LTP of the perforant path projection from entorhinal cortex to hippocampus causes BDNF release in the hippocampus and CREB activation in the entorhinal cortex, as does infusion of BDNF directly into the hippocampus [55,56]. Furthermore, BDNF is involved in retroaxonal modulation of input synapses in *Xenopus* development [17].

We have hypothesized that retroaxonal signals can stabilize recent synaptic changes, but should emphasize that they would be one of many signals to do so. For example, neuromodulators have been shown to facilitate L-LTP [57,58]. Ascending neuromodulatory neurons fire at increased rates during times of alertness [59,60], and might cause long-lasting expansion of the neural populations representing stimuli present at these times [61]. Control of synaptic stability by neuromodulatory systems would have the advantage of fine temporal specificity, because it relies on fast action potential-mediated signals, rather than slow retroaxonal signals. However, because of the diffuse nature of neuromodulatory projections, this mechanism would not be able to select between simultaneously active neurons, such as those representing different visual features simultaneously present in the same image [9]. It is therefore intriguing that the signaling pathways activated by neuromodulators and neurotrophins overlap [62–65]. Working in concert, neuromodulatory and retroaxonal signals might thus allow temporally precise and cell-specific control of input stabilization.

Neuronal selection during adult learning: the stability of the fittest

The discovery of cell death during nervous development led to the idea that a form of darwinian competition selects those neurons that will best serve the animal in future life [30,31]. The benefit of a neuron to the organism is determined by its ability to supply its synaptic targets with appropriate information. If developmental processes produce neurons of diverse connectivity patterns, these neurons will perform diverse information-processing functions. Competition for retrograde neurotrophic factors would ensure that the neurons that produce information best suited for their targets – and thus form the most outputs – would be preferentially selected for survival and growth.

In this article, we suggest that an analogous competitive process could occur during adult learning. In adulthood, neuronal death is rare. We hypothesize, however, that retroaxonal signals could facilitate learning by promoting not neuronal survival but the stabilization of recent changes to input synapses. We now illustrate this idea with reference to some recent recordings from the hippocampus. What follows is hypothesis, not proven fact. However, we hope the use of a specific context helps explain the ideas clearly.

Stability of hippocampal place fields

When rats perform spatial behaviors, hippocampal pyramidal neurons fire in restricted regions of space known as 'place fields.' To investigate the formation of place fields, Frank and colleagues [5] recorded CA1 pyramidal neurons while rats explored an environment which was largely familiar, except for one novel region that was previously inaccessible. When rats were allowed to explore the novel region, place fields formed within minutes, and on the first day of recording there were approximately twice as many place fields coding for the novel region as the familiar part of the apparatus. These were not newborn neurons, as adult neurogenesis does not occur in CA1; instead, the new place fields had come to 'inhabit' existing neurons. However, most of these new inhabitants did not stay for long – after 3 days of exploration of the new environment, the density of place fields in the novel region was down to that of the familiar region. Whatever changes caused the appearance of the new place fields must have in most cases reversed after a few days, persisting only in a subset of neurons.

What determines whether a new place field is stabilized or decays? Important information on this question has been provided by studies in mice by Kentros and colleagues [66–68]. Unlike with rats, the place fields in mice are frequently unstable even in familiar environments. However, when mice were performing a task that required active spatial navigation – rather than simply collecting food pellets – place fields could remain stable over multiple days of recording. This suggests that the stability of a place field might correlate with the utility of the information it carries for performance of behaviors. In support of this idea, place field densities can be elevated in regions of space that are relevant for behavioral performance, such as goal locations [69].

On the basis of these experiments, we suggest the following scenario. When an animal is placed in a novel environment, several new place fields form. This process presumably involves plasticity of the input synapses of neurons expressing new place fields. Typically, these synaptic changes decay, and the new place field disappears. However, several factors can cause these changes to stabilize. One such factor is retroaxonal signals caused by strengthening of output synapses. If spikes fired when the animal is in the new place field are coincident with spikes of downstream neurons (which must therefore fire in the same region of space), connections onto these cells

will be strengthened. If enough of the cell's output connections are strengthened, the resulting retroaxonal signals will be sufficient to stabilize the recent changes to the cell's input synapses, and the new place field will persist. In this way, those cells whose connection patterns best enable them to join a coherent network representing the novel location will have their place fields stabilized. If the information carried by this network is behaviorally relevant, synapses from these cells to behavior-producing circuits will also be strengthened, thereby encouraging the further stabilization of the network. If synapses onto behavior-producing circuits are not formed, however, stabilizing signals passed within the cells of the network might not be sufficient to ensure its continued maintenance, causing the representation of the new information to be lost. In this way, information that is relevant to producing behavior will be specifically retained, at the expense of information that is behaviorally irrelevant.

Other examples

We have introduced this idea in the context of hippocampal place fields; however, these mechanisms might operate in many systems. For example, in monkeys trained to categorize visual stimuli according to one of two stimulus dimensions, neurons of inferotemporal cortex developed a stronger representation of the dimension relevant to categorization, even though the only change was the behavioral associations, and the set of stimuli presented was the same [9,10]. This suggests that a mechanism exists for selecting those changes to receptive fields that are most relevant to discrimination performance. We suggest that during learning of the task, individual cortical neurons develop representations of diverse features of the visual stimuli. Neurons encoding features relevant for behavior will strengthen more synapses onto downstream motor-related circuits than neurons encoding irrelevant information. This in turn causes recent changes to input synapses to be stabilized selectively on neurons encoding behaviorally relevant features, and a neural representation adapted to the particular task to develop.

In the prior example from hippocampus, the appearance of a new place field is a sudden event. In other systems, changes in receptive fields might take place gradually. In this case, retroaxonal signals could then select which of these small changes should be kept, resulting in a progressive fine-tuning of population codes. Interestingly, a recent study [70] found that motor cortical tuning curves show small random shifts even in the absence of learning; when subjects learned to compensate for novel forces, shifts in tuning curves were of a similar magnitude to the control case but showed a systematic bias in direction, consistent with the selective stabilization of beneficial changes from several otherwise transient alterations in receptive fields.

Conclusion

Based on the above data, we hypothesize the following scenario. During learning, many neurons exhibit changes in their input connections, leading in turn to changes in the information carried by their spike patterns. These changes are guided by 'feedforward' principles such as Hebb's rule which make the resulting connection patterns more likely to extract useful information than purely random changes [71,72]. Nevertheless, much of the time the new spiking patterns do not carry information useful for downstream targets, in which case output synapses will not be strengthened, and the changes to input connections will decay. In some cases, however, such as when a neuron decodes behaviorally relevant information, output synapses are strengthened, and the neuron receives a retroaxonal reinforcing signal that stabilizes its recent input changes. At times of heightened alertness, the activity of ascending neuromodulatory systems provides a second reinforcing signal; stabilization of input synapses will be greatest when the neuron receives both reinforcing signals.

We conclude with an analogy, between the community of neurons in the brain and the community of humans in science research. The benefit of a scientist to the greater community is determined by their ability to extract useful information from experimental data and to communicate it to a wide audience. At early developmental stages, a scientist's career survival depends on achieving a wide enough audience for the information they produce, as measured for example by citation counts. After tenure, survival is assured, but competition continues. If the scientist has a new idea that generates a widely cited paper, it will encourage them to continue working along similar lines. An idea that did not generate interest, on the other hand, will soon be discontinued.

These types of social interactions occur not only in science but in many fields of human endeavor where multiple decision-making individuals work toward a common goal. This might not be a coincidence; such interactions often result in a productive, self-organizing allocation of individuals to tasks, without the need for a central point of coordination. We suggest that analogous interactions between neurons allow them to coordinate their work toward ensuring the survival and reproduction of the host organism.

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