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COMMENT*

Neuronal regulation versus synaptic unlearning in memory maintenance mechanisms

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Abstract. Hebbian learning, the paradigm of memory formation, needs further mechanisms to guarantee creation and maintenance of a viable memory system. One such proposed mechanism is Hebbian unlearning, a process hypothesized to occur during sleep. It can remove spurious states and eliminate global correlations in the memory system. However, the problem of spurious states is unimportant in the biologically interesting case of memories that are sparsely coded on excitatory neurons. Moreover, if some memories are anomalously strong and have to be weakened to guarantee proper functioning of the network, we show that it is advantageous to do that by neuronal regulation (NR) rather than synaptic unlearning. Neuronal regulation can account for dynamical maintenance of memory systems that undergo continuous synaptic turnover. This neuronal-based mechanism, regulating all excitatory synapses according to neuronal average activity, has recently gained strong experimental support. NR achieves synaptic maintenance over short time scales by preserving the average neuronal input field. On longer time scales it acts to maintain memories by letting the stronger synapses grow to their upper bounds. In ageing, these bounds are increased to allow stronger values of remaining synapses to overcome the loss of synapses that have perished.

1. Introduction

In a recent Viewpoint article, van Hemmen [1] has reviewed problems caused by Hebbian learning in some memory models, and the unlearning method that resolves them. Unlearning, in this context, is the idea of applying Hebbian learning with a reversed sign to undesired states, such as spurious mixed states in a Hopfield model [2]. This idea was put forward in 1983 by Crick and Mitchison [3] and by Hopfield *et al* [4]. In his review paper, van Hemmen discusses the motivation of this approach and describes the reasons for its success. He puts unlearning in the larger context of eliminating undesirable global correlations between memories and performs thorough simulations to substantiate the theory. Nonetheless, the simulations cannot be extended to the biologically interesting case of low coding. Moreover, the problem of spurious states is absent in models of sparse coding.

The one situation that may need a cure of an unlearning type is the case of pathologic attractors [5, 6]. This concept refers to memories in an associative memory model that possess anomalously large basins of attraction. An associative memory system that performs

* This article was submitted to *Network: Computation in Neural Systems* as a response to the recent Viewpoint by van Hemmen [1]. In their Comment, Horn, Levy and Ruppin argue for the mechanism of neuronal regulation in associative memory models as an alternative to the mechanism of unlearning discussed by van Hemmen. To obtain a complete picture of the advantages and disadvantages of both types of mechanism, readers should also consult van Hemmen's original article. *Editor-in-Chief*

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free recall from random stimuli, and then learns in a Hebbian fashion the memories it recalls, can fall into a pathologic behaviour in which some basins of attraction grow too strongly and overshadow all other memories. Obviously this should be avoided in functional memory systems. We have presented [7] a novel solution to this problem, based on a *neuronal regulation* (NR) mechanism that acts to maintain neuronal activity. This mechanism operates in conjunction with random activation of the memory system, and is able to counterbalance degradation of synaptic weights. At the same time, it normalizes basins of attraction of memories, thus preventing the creation of pathologic attractors.

Activity-dependent neural regulatory processes have previously been observed experimentally [8] and studied theoretically [9, 10]. The main new feature introduced in our work is the view of NR as a common change in the synaptic efficacies of a neuron that, depending on the neuron's activity, keeps the relative weights of different synapses unchanged. This key feature has recently received direct experimental support from the work of Turrigiano *et al* [11], suggesting that neocortical pyramidal neurons regulate their firing rates by scaling the strength of their synaptic connections up or down as a function of activity. This is a slow process, affecting AMPA-type receptors that mediate excitatory synaptic transmission. Just as in the model [7], it produces regulation in the desired multiplicative postsynaptic fashion.

In section 2 we describe our model briefly. We show that there exists an analogy between NR and unlearning, as both mechanisms weaken memories that are too strongly retrieved. However, in contradistinction to unlearning, NR does not involve an anti-Hebbian synaptic mechanism. Instead, it employs a neuronal mechanism, acting simultaneously on all its dendritic synapses, ensuring homeostasis of memory systems. Section 3 is devoted to long-term maintenance. When synapses are no longer kept at their original values, memories can nonetheless be maintained intact. In section 4 we review pathologies that arise when neuronal regulation fails (dementia) or when it acts under wrong conditions, as in a model of schizophrenia. We contrast the achievements of NR with the results of synaptic unlearning in section 5, and discuss the possible implementation of NR in sleep.

2. Neuronal regulation

2.1. Short-term maintenance

As a platform for the formulation and testing of our approach, we use the neural network model of Tsodyks [12], taking it to represent a module of associative cortex in which a set of memories is engraved. The model includes N excitatory neurons that encode M memory patterns with sparse coding level $p \ll 1$. The effect of inhibitory neurons is represented by global inhibition that is proportional to the overall activity of the excitatory neurons. In accordance with the conventional Hebbian rule, the synaptic weight J_{ij} projecting from neuron j to neuron i, following the consecutive storage of M memory patterns η^μ, is

$$J_{ij} \doteq \frac{1}{Np} \sum_{\mu=1}^{M} \eta_i^\mu \eta_j^\mu . \tag{1}$$

The dynamics of retrieval is given by

$$V_i(t' + \Delta t') = \mathcal{S}\left(h_i(t') - T\right) \tag{2}$$

where V_i is the activity of the ith binary neuron, t' denotes the fast time scale of network updating in a single retrieval trial, and T is the threshold. $\mathcal{S}(x)$ is a stochastic sigmoid

function, taking the value 1 with probability $(1+e^{-x})^{-1}$ and 0 otherwise, and

$$h_i(t') = h_i^e(t') - \frac{\gamma}{Np}\sum_j^N V_j(t') + I_i \tag{3}$$

is the membrane potential. It includes the excitatory Hebbian coupling of all other excitatory neurons,

$$h_i^e(t') = \sum_{j\neq i}^N J_{ij}V_j(t') \tag{4}$$

an external input I_i, and inhibition that is proportional to the total activity of the excitatory neurons.

In the model, the synaptic weight matrix undergoes two types of changes. One is $J_{ij} \to (1-\epsilon_{ij})J_{ij}$, due to synaptic turnover, represented here by a deterioration factor ϵ_{ij} that is synapse specific and is newly chosen at every deterioration cycle in a random fashion (with mean ϵ and variance σ^2). The second type of change is the NR effect, multiplying each synaptic weight at every NR cycle by $J_{ij} \to c_i J_{ij}$. Note that this corrective action is neuron specific, i.e. c_i is determined by the postsynaptic neuron i, multiplying all the synapses on the dendritic tree of neuron i by the same factor. c_i itself is chosen to be slightly larger (or smaller) than 1, according to whether the average input seen by neuron i in the NR cycle is weaker (or stronger) than a specified baseline value. This is the same type of regulation that has recently been suggested experimentally [11]. The definition of c is given by

$$c_i = 1 + \tau \tanh\left[\kappa\left(1 - \frac{\langle h_i^e(t)\rangle}{H_i^e}\right)\right] \tag{5}$$

where $H_i^e = \langle h_i^e(t=0)\rangle$ and κ and τ are rate constants. To measure the neuronal average input, random excitations of the memory system are invoked, indicating to each neuron the size of its overall synaptic degradation, on which it can base its appropriate corrective measure c_i.

The NR mechanism can counter-balance the average deterioration of the system, and works nicely as long as the accumulated variance is small. We have run it [7] on a system that undergoes consecutive cycles of Hebbian learning, synaptic degradation and neuronal regulation. We found that it performs very well, maintaining both old and new memories, and storing all of them with roughly the same strength, i.e. similar basins of attraction.

In our calculations we have to make a clear distinction between Hebbian learning and neuronal regulation periods. In Nature we assume that the two correspond to different modes of activity in the brain. While the Hebbian process modifies the single synapse the NR mechanism modifies all synapses of the (postsynaptic) neuron concomitantly.

2.2. Experimental evidence

The recent results of [11] point out an experimental behaviour which is very much in the spirit of the NR model outlined above. They show that on blocking the neural activity in a cortical culture, the amplitude of miniature postsynaptic currents (mEPSCs) increases. If, on the other hand, inhibition is blocked, thus increasing the activity, the mEPSC amplitudes will decrease until firing rates return to baseline values. Thus, the neuron is able to keep its firing rate at a steady-state value irrespective of external input changes. This could work through up or down regulation of excitatory AMPA-type receptors. Moreover, it is a multiplicative effect, just as expected from the neuronal regulation factor of equation (5). This type of

synaptic plasticity was observed over periods of up to 48 hours. We may thus conclude that NR and Hebbian learning are two different synaptic modification mechanisms: NR is a slow, neuron-specific process that directly modifies AMPA-mediated conductance, while Hebbian learning (i.e. LTP/LTD) is carried out by fast, NMDA-dependent synapse-specific processes.

Homeostatic mechanisms controlling synaptic efficacies were also recently reported by Davis and Goodman [13]. Working on genetically manipulated muscle innervation in the *Drosophila* they have observed a compensatory change in quantal size at the neuromuscular junction that is anti-correlated with the increase or decrease of the innervation, as would be expected from the action of NR processes. In addition there exists evidence [14] that, during the formation of the neuromuscular junction, weak synapses are eliminated while stronger ones are retained. This is in agreement with our ideas concerning long-term maintenance that are discussed in section 3.

2.3. Normalization of basins of attraction

Homeostasis of neuronal baseline activity ensures that all memories have a similar basin of attraction, as otherwise some neurons that belong to the stronger memories would be more active than others. To demonstrate this property we display in figure 1 a case of 50 memories, a few of which start out with different basins of attraction because their coding level p is less sparse than that of the rest.

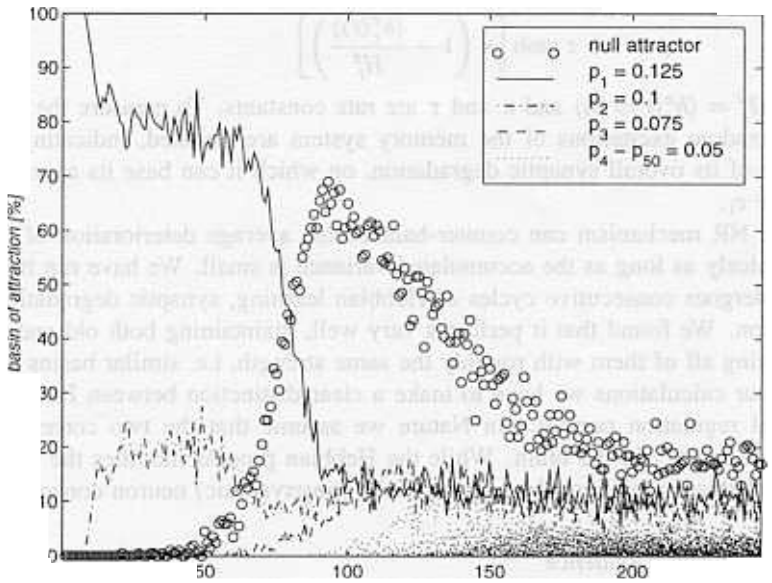

Figure 1. Regulation of the size of basins of attraction with mixed coding levels. In this simulation of $M = 50$ memories in a system of $N = 1000$ neurons some of the memories have different coding levels. This system undergoes synaptic degradation and NR cycles, without any Hebbian learning, leading to homogenization of the basins of attraction. The different symbols refer to the leading memories and to the null attractor. The latter is the only attractor in this system other than the memories. It corresponds to the state of total quiescence. Its basin of attraction grows and then diminishes as the process continues. After 200 simulation steps the basins of attraction of the memories are much more homogeneous than at the start.

We find this property to be particularly important since it explains how one may avoid the creation of pathologic attractors. It allows one to train an associative memory model using different memory strengths and durations during the Hebbian paradigm, and let the NR phase regulate the result into a homogeneous and well balanced memory system.

3. Long-term maintenance

Synaptic maintenance by NR fails if the variance of synaptic deterioration becomes too strong. Even if each deterioration step has small variance, the cumulative variance will increase with time leading eventually to the demise of the system. Thus one may define a critical time [7] that decreases rapidly with increasing σ, beyond which the spread of the synaptic weights that arises from the deterioration process becomes so wide that the system loses its memories. There exists, however, a remedy to this problem: putting an upper bound on synaptic weights. This is displayed in figure 2, where we test a system with large variance of synaptic degradation, that causes fast deterioration in memory retrieval performance unless synapses are appropriately bounded. We find [7] that, for appropriate synaptic upper bounds, the network may successfully maintain its stored memories forever even in the face of ongoing, continuous, synaptic turnover. The simple intuitive explanation is that, by letting the process of degradation and maintenance continue for a long time, the synapses undergo a random walk process with bounds. If the synaptic bound is sufficiently low, the number of large synapses retained by the NR mechanism will be higher than the minimal number of synapses required to maintain memory performance. By maintaining the neurons' average postsynaptic potentials, the NR mechanism preserves the number of large synapses practically forever, even though the identity of these synapses may change during the network's lifetime.

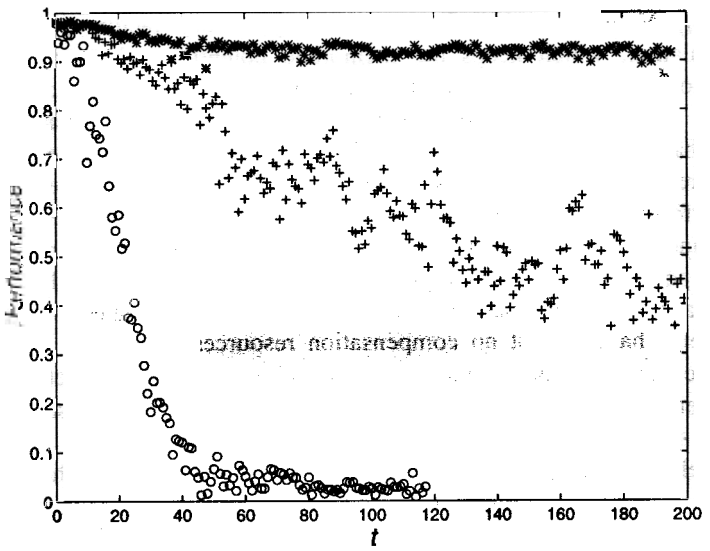

Figure 2. The effect of synaptic bounds. The small circles denote the performance of the network without synaptic bounds. The + symbols denote the performance of the network with an upper bound of $8/Np$ (i.e. 8 times the size of a synapse that stores one memory at $t = 0$), while the $*$ symbols correspond to an upper bound of $3/Np$. The other parameters of the simulation are $N = 500$, $M = 25$, $p = 0.075$, $\epsilon = 0.005$, $\sigma = 0.2$. For further details, see [7].

The possibility that the network can achieve stability, i.e. that it continues to exhibit high retrieval performance forever, is further enhanced when a 'viability' bound is incorporated. In this case, synapses whose values decrease below some lower bound die and their values are set to zero. This NR-induced selective synaptic death process helps preserve the network's performance because synapses with large initial values (i.e. synapses that encode several memories) have greater chances to survive than synapses with small initial values. The former are clearly more significant. This intuitive notion, supported by the work of Sompolinsky [15] on clipped synapses, has recently been proven formally by Chechick *et al* [16].

4. Neuronal regulation and its failure in the ageing and the ailing brain

The regular synaptic turnover processes take a turn for the worse in the ageing brain, which has to cope with synaptic depletion, a considerable synaptic loss in various cortical regions. NR in this case is manifested by an increase of synaptic sizes, which we interpret as an increase in the upper bounds on synaptic values, reflecting a functional compensatory increase of synaptic efficacy [17–19]. The combined outcome of these counteracting synaptic degenerative and compensatory processes can be evaluated by measuring the total synaptic area per unit volume (TSA). The latter correlates strongly with cognitive ability. For patients with Alzheimer's disease (AD) one finds that the TSA decreases as the disease progresses [18, 20–22], pointing to the important role that pathological synaptic changes play in the cognitive deterioration of AD patients.

This raises the interesting possibility that disturbances of NR mechanisms may underlie the clinical manifestations of Alzheimer's disease [23], explaining the onset of dementia. In the model of [23] a fraction d_i of the input synapses to each neuron i are deleted, and are compensated for by a factor c_i which each neuron adjusts individually. This is equivalent to performing the replacement $J_{ij} \rightarrow c_i w_{ij} J_{ij}$ where w_{ij} is either 0 or 1, and $\sum_j w_{ij}/N = 1 - d_i$. The local compensatory factor c_i is determined via neuronal regulation, which keeps the membrane potential and neural activity at their original, premorbid levels; that is, NR must now compensate for the accumulative deletion of synapses. Our working hypothesis was that the NR-based synaptic compensatory mechanisms that in normal ageing succeed in preserving a considerable level of cognitive functioning are disrupted in AD. Numerical simulations have allowed us to study the network's performance at various NR (compensation) rates. The performance level is better maintained if the compensation rate is high. As reviewed in [24], young and very old AD patients suffer from rapid clinical deterioration, while the majority of AD patients have a more gradual pattern of decline. These clinical patterns may arise because very old patients have almost no compensation resources and young patients have very potent synaptic compensation mechanisms. Interestingly, studies of reactive synaptogenesis following experimental hippocampal deafferentation lesions in rodents show that the rate of compensatory synaptogenesis decreases as a function of age [25, 26].

Our modelling studies have shown that even if the NR mechanisms are intact, pathologies may arise if the system in which they operate changes in a way that the mechanism was not designed to control. In [6] we studied a computational model of Stevens' theory of the pathogenesis of schizophrenia [27]. This theory hypothesizes that the onset of schizophrenia is associated with reactive synaptic regeneration occurring in frontal regions receiving degenerating temporal lobe projections. These synaptic changes are modelled in the framework of a 'frontal' associative memory network whose internal synapses are strengthened in response to weakened input synapses representing incoming

temporal projections. Superimposed on these alterations, we incorporated an enhancement of activity-dependent synaptic changes, to model the hypothesized effects of increased dopaminergic activity observed in schizophrenia (see [6] for more details). As a result of these alterations, the network begins to spontaneously retrieve memory patterns even in the absence of any input retrieval cues, as demonstrated in figure 3. This figure traces the distribution of the memory patterns to which the network has spontaneously converged after the assumed pathological alterations are induced. The total frequency of convergence to memory patterns increases as time evolves. The distribution of the memory patterns spontaneously retrieved tends to concentrate on a single memory pattern as more trials occur. Although the synaptic matrix was initially non-biased, small random correlations between the network's initial states and a few of the memory patterns are sufficient to overwhelmingly and 'pathologically' enhance their retrieval. We therefore see that biased retrieval is formed, and out of the many patterns stored in the network only very few are actually spontaneously retrieved. This pathologic attractor formation of biased spontaneous retrieval can account for the occurrence of schizophrenic delusions and hallucinations without any apparent external trigger, and for their tendency to concentrate on a few central cognitive and perceptual themes. The model presented in [6] also explains why schizophrenic positive symptoms tend to wane as the disease progresses, why delayed therapeutical intervention leads to a much slower response, and why delusions and hallucinations may persist for a long duration.

The demonstration of pathologic attractor formation in schizophrenia points to the importance of preventing the latter in normal processing. This protective task is probably

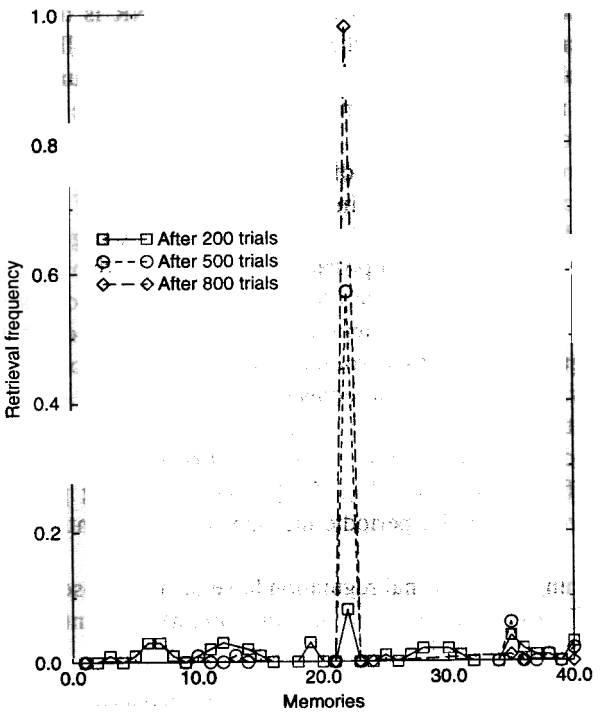

Figure 3. Distribution of spontaneous memory retrieval. The positive feedback that comes about from regulatory compensation, Hebbian learning and random activation, leads to the emergence of pathologic attractors. The x-axis enumerates the memories stored, and the y-axis denotes the retrieval frequency of each memory. For details, see [6].

carefully regulated, and depends on a rather delicate balance between neuronal regulation and the level of activity-dependent synaptic changes (i.e. synaptic plasticity and learning). It further emphasizes the importance of keeping neuronal regulation and learning segregated. Random activation of memories combined with Hebbian learning will lead to a positive feedback loop that ends up with pathologic attractors.

The possible involvement of NR in both AD and schizophrenia can explain the age difference in the appearance of these disorders. Elderly people are more likely to suffer from decreased compensatory resources and NR dysfunction, and hence AD is typically a disease of the old. In contradistinction, in response to a pathologic disconnection between various cortical regions, normal functioning NR can lead to the emergence of spontaneous activation of cortical networks and to the subsequent formation of pathologic attractors. In fact, ailing NR mechanisms will fail to cause spontaneous cortical activation, explaining why schizophrenia (more specifically, its psychotic positive symptoms) is typically a disorder of the young.

5. Discussion

The different facets of neuronal regulation extend over different time periods. The basic NR mechanism of section 2 occurs both in the developing brain as well as in the mature brain over daily periods. Development over periods of years fits into the description of long-term maintenance of section 3, where the original synaptic efficacies are no longer maintained and the stronger synapses survive. Finally, ageing brings with it the phenomenon of synaptic deletion, which can be coped with provided the potential for NR is there and the system has not yet reached its critical capacity. Otherwise dementia will follow, as described in section 4. Neuronal regulation thus presents an attractive and quite unique opportunity to address a broad range of normal and altered memory-related cognitive functioning within a common, simple framework.

Neuronal regulation relies on activation of the memory system by random inputs, thus testing all basins of attraction without requiring explicit knowledge of the memory patterns themselves. As suggested in [3, 4], such random activation may be triggered by PGO waves [28] during REM sleep. NR is therefore a possible realization of 'dynamic stabilization', a term that describes the idea that during sleep there exist dynamic processes that maintain synaptic efficacies [29]. Note that in our approach we have to segment between Hebbian learning and neuronal regulation. The two processes, although being complementary, cannot take place simultaneously. This segregation seems to fit nicely with the existence of different stages of sleep that may thus subserve both memory consolidation and neuronal regulation. These two functional modes of the brain may be regulated by the different neuromodulators that are dominant in different stages of sleep [30]. The alternating phases of REM and non-REM sleep may serve as a regular periodic mechanism implementing NR in a gradual, corrective manner.

Both Hebbian unlearning and neuronal regulation have been proposed as complementary mechanisms to Hebbian learning. They differ on some important points and are similar on others. Let us begin by noting their distinctive features:

- Originally, Crick and Mitchison [3] and Hopfield *et al* [4] have suggested that unlearning serves to eliminate spurious attractor states and thus increase the memories' basins of attraction. However, while spurious states are abundant in the Hopfield model, they occupy only a small fraction of the retrieval scene of the more biologically realistic low-coding memory networks (e.g. [7]).

- Neuronal regulation is a vital mechanism for counteracting the formation of pathologic attractors and for achieving long-term memory maintenance. While it is conceivable that unlearning may also serve to efficiently counteract the formation of pathologic attractors, it cannot cope with the problem of synaptic turnover and cannot act as a memory maintenance mechanism.
- Computationally, there is an important advantage to using NR rather than anti-Hebbian synaptic unlearning: the NR mechanism regulates itself, unlike unlearning that needs an external agent to turn it off after a certain optimal number of unlearning cycles.
- Biologically, while there is a rising body of recent experimental evidence testifying that NR takes place in both the peripheral and central nervous systems, the experimental support for unlearning has been fairly scarce.

Both unlearning and neuronal regulation prevent the generation of pathologic attractors and rely on random activation of memories. Unlearning has the advantage that it is able to increase the memory capacity of the intact network, while NR mainly works to preserve the existing capacity of a network undergoing synaptic turnover and degradation. Hence, the possibility that both mechanisms may coexist should not be ruled out. As shown by van Hemmen, by eliminating global correlations unlearning serves to store many patterns with varying activities. As shown here, NR may serve the same goal by homogenizing the basins of attraction of patterns with mixed coding levels (figure 1). It may well be, however, that both unlearning and NR are insufficient for efficient storage of memories with coding levels that differ by an order of magnitude. For this task, we have recently shown [31] that a multi-modular network is clearly advantageous. Its architecture is based on segregation between inter-modular synaptic couplings and intra-modular ones, with the latter undergoing nonlinear dendritic processing.

Further experimental studies are needed to evaluate how the findings of Turrigiano *et al* [11] of NR in the developmental stage carry on to adults. However, the instrumental potential of NR in obtaining memory maintenance, coupled with morphometric evidence showing that the average total synaptic area per unit volume is maintained throughout normal ageing [32, 17], make it highly likely that NR plays an important functional role in adulthood too.

In summary, we conclude that neuronal regulation is a natural and plausible candidate for performing homeostasis of memory systems. Its common feature with unlearning is that it reduces basins of attraction that are too large, a very important property for keeping memory systems well balanced. It replaces synaptic unlearning by a neuronal-based process, that complements Hebbian synaptic learning. Hebbian learning and neuronal regulation can occur in a segmented and intertwined fashion, relying on different modes of activation of the brain. They can go on without end, which is suitable for describing lifelong human processes.

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