Synaptic clustering or scattering? Insight from a model of synaptic plasticity in dendrites

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Abstract

A large body of theoretical work has shown how dendrites can increase the computational capacity of the neuron. This work predicted that synapses active together should be close together in space, a phenomenon called synaptic clustering. Experimental evidence has shown that, in the absence of sensory stimulation, synapses nearby on the same dendrite tend to be active together more than expected by chance. Synaptic clustering, however, does not seem to be ubiquitous: other groups have reported that nearby synapses can respond to different features of a stimulus during sensory evoked activity. In other words, synapses that are active together during sensory evoked activity can be far apart in space, a phenomenon we term synaptic scattering. To unify these apparently inconsistent experimental results, we use a computational framework to study the formation of a synaptic architecture – a set of synaptic weights – displaying both synaptic clustering and scattering. We present three conditions under which a neuron can learn such synaptic architecture: (i) presynaptic inputs are organized into correlated groups of neurons; (ii) the postsynaptic neuron is compartmentalized in subunits representing dendrites; and (iii) the synaptic plasticity rule is local within a subunit. Importantly, we show that given the same synaptic architecture, synaptic clustering is expressed during spontaneous activity, i.e. in the absence of sensory evoked activity, whereas synaptic scattering is present under evoked activity. Interestingly, reduced dendritic morphology in our model leads to a pathological hyper-excitability, as observed for instance in Alzheimer's Disease. This work therefore unifies a seemingly contradictory set of experimental observations: we demonstrate that the same synaptic architecture can lead to synaptic clustering and scattering depending on the input structure.

Author Summary

Neurons connect together through synapses which are distributed on dendrites. The spatial distribution of active synapses on the tree-shaped dendrites is under debate. Do active synapses cluster or scatter on dendrites? Experimentalists observe both types of spatial distributions depending on the presence/absence of a sensory stimulus. Our modelling study explains how the two distributions can co-exist within a single learned synaptic architecture, and we observe in our model clusters/scatters in the absence/presence of a sensory stimulus. We further show that the same learning mechanism can lead to a maladaptive outcome. When the number of dendrites

decreases, as observed in Alzheimer's Disease, neurons become hyper-excitable. This result sheds a new light on the link between dendrites and neuropathologies.

Introduction

Dendrites have the potential to ehance the computational capacity of the individual neuron. Modeling studies have shown that dendrites allow neurons to perform complex computations which could not be achieved by single compartment neurons [1, 2]. In particular, dendrites have been proposed to enhance sound coincidence detection [3], to play a role in binocular disparity [4], and to help to compute the angular tuning in the barrel cortex [5]. The first models of dendritic computation predicted the existence of synaptic clustering [6–8], that is, nearby synapses on the same dendritic branch are active together, a property that was at that time rather surprising (see Fig. 1A for illustration). Since then, several experimental studies have examined how active inputs are organized onto dendrites. The picture remains, however, rather confusing: on the one hand, Takahashi et al. [9] observed synaptic clustering in adults rats without sensory stimulation. Kleindienst et al, using organotypic slices from neonatal rats, reported that NMDA receptors contribute to the expression of synaptic clustering [10]. On the other hand, during sensory stimulation, synaptic scattering has been reported several times [11–14], as shown in Fig. 1C. For instance, two nearby synapses on the same sensory neuron can have different stimulus tuning (Fig. 1D), suggesting that while one is active for a given stimulus the other is inactive and vice-versa [12]. Observations made in multiple sensory modalities including touch [11], vision [13], and hearing [15] suggest that synaptic scattering is typical of a sensory episode. We wondered whether these apparently contradicting pieces of evidences, i.e. synaptic scattering and clustering, can be reconciled within one theoretical framework.

To this end, we developed a computational model to study the formation of a synaptic architecture that could either lead to synaptic clustering or scattering within the same neuron. The model consists of inputs that project to a neuron with different subunits, mimicking different dendritic branches. We hypothesized that different types of activity lead to different input correlations: during spontaneous activity (i.e. absence of stimulation), a given set of inputs are correlated, whereas during evoked activity, another set of inputs are correlated. This assumes that the stimulus is encoded into correlation, as opposed to only firing rates [16–18].

Synaptic plasticity shapes the weights, such that a single synaptic architecture can be consistent with both effects: the neuron shows synaptic clustering under spontaneous activity, whereas it leads to synaptic scattering under evoked activity. We showed that synaptic inputs, which triggered the highest response are the ones that are scattered over the dendritic compartments. The neuron therefore responds maximally to novel stimuli. Finally, we studied how the synaptic architecture depends on dendritic morphology. We found that if the dendritic structure is reduced, the neuron may develop seizure-like activity, a scenario present in different disease cases such as Alzheimer's disease [19]. In summary, we provide a unifying computational framework which reconciles apparently disparate experimental findings on synaptic clustering and scattering, uncovering mechanism and function of synaptic architecture in dendrites.

1 Results

A learned synaptic architecture leading to synaptic clustering under spontaneous activity. In this section we investigate how learning can generate a synaptic architecture consistent with synaptic clustering. Three elements govern the

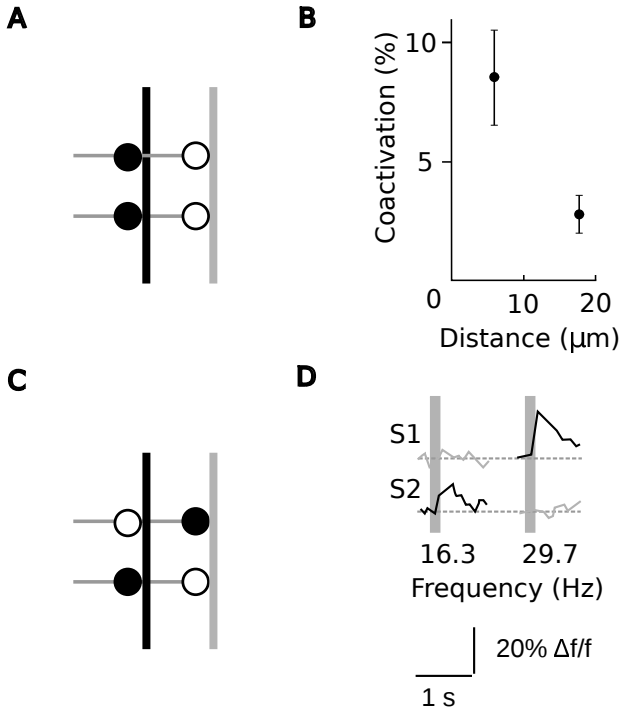

Figure 1. Synaptic clustering and synaptic scattering. **A**. Schematic representation of four synapses (circles) impinging on two spatially or temporally distinct locations on dendrites. Nearby synapses on the same dendritic branch co-activate (black:active/grey:inactive) during spontaneous activity, the so-called synaptic clustering. **B**. Measurements of spine co-activation probability in hippocampal pyramidal neuron slices. The probability is high for spines closer than 10 microns and significantly lower otherwise. Replotted using data from Kleindienst et al 2011. **C**. We posit that during sensory stimulation, synaptic events occur at distinct spatial or temporal locations. Synapses activate in an anti-clustered fashion. **D**. Calcium response from two spines on a pyramidal neuron recorded in vivo (here are shown two trials corresponding to two different sound frequencies). Replotted using data from Chen et al 2011.

evolution of synaptic weights: pre-synaptic inputs, a post-synaptic neuron, and a learning rule. We therefore analyze how these three elements combine to develop a synaptic architecture such that the neuron exhibitis synaptic clustering as experimentally observed [9].

To learn such a synaptic architecture, we used (i) a learning rule that is local to a single subunit, (ii) a multi-subunits binary neuron model, and (iii) presynaptic inputs organized in correlated groups of neurons. To construct those inputs, we bin the spike trains and divide the bins into two types: bins where neurons fire with a given probably, leading to Poisson statistics, and events where all the neurons from a group fire (see Materials and Methods). These events are there to mimic the synchronous activity observed in thalamic inputs [20, 21], and assume these inputs being under spontaneous activity. In Fig. 2A, we present an example in which events occur in two independent groups of neurons. Importantly, these events are uncorrelated between the two groups. These populations of presynaptic input project onto a neuron model where integration happens in two stages, similar to the two-layer neuron model developed by Poirazi et al. [8]. We show this model in Fig. 2B. Synaptic inputs are first integrated within their distinct dendritic subunit, each independently performing a weighted sum filtered by the function D to account for dendritic non-linearities (see Materials and Methods). This operation results in a local variable $v_j = D\big(\sum_i w_{i,j} x_i\big)$ where x_i is the activity of the ith pre-synaptic neuron (being either 0 or 1) and $w_{i,j}$ is the local synaptic weight from the ith neuron to the j dendritic subunit. v denotes a local signal that could be the membrane potential or the calcium concentration. The learning rule uses the local signal to the j^{th} subunit to compute the weight change $\Delta w_{i,j} = \alpha(2x_i - 1)v_j$ where α is the learning rate. These three elements combine to generate a unique synaptic architecture.

To study the evolution of synaptic weights in this model, and to illustrate the fixed point of the dynamics, we used two-dimensional flow diagrams. We tracked the evolution of two parameters C1 and C2 that are respectively the mean synaptic weights of the first and the second group of inputs. Each arrow in the diagram shows the average weight change. We first analyzed a system where presynaptic inputs are uncorrelated (Fig. 3A). We analytically calculated the average weight evolution (see Materials and Methods). In this case, both mean synaptic weights tend to depress, leading to a silent neuron. The situation changes dramatically when presynaptic inputs have some degree of correlations, i.e. synchronous events within the two different pools (Fig. 3B). In this case, depending on the initial weight distribution, either the first (C1) or the second (C2) group of synaptic weights are potentiated, while the other is depressed, as a result of symmetry breaking [22]. The inset in Fig. 3B shows the most probable evolution of the synaptic weights given two initial conditions (D1 and D2). These initial conditions and the noise dictate which set of weights are potentiated. This results in a group of potentiated synapses corresponding to one group of neurons, while synapses from the other group are depressed.

We then simulated a neuron with two dendritic subunits. In each subunit, synaptic weights started from a different initial condition (D1 or D2). Consistent with the flow diagram analysis, we showed that synapses from the first group are potentiated, and synapses from the second group are depressed, onto the first subunit; likewise on the second subunit synapses from the second group are potentiated and synapses from the first group are depressed. The final synaptic architecture is shown in Fig. 3C. If the initial conditions are random, which of the groups develops strong synapses onto a given dendritic branch is random, and therefore with two branches, 50% of the time, the two dendritic branch have the same selectivity and 50% of the time, the selectivity is different.

We then tested whether this synaptic architecture is consistent with synaptic clustering. We computed the co-activation probability of this neuron under spontaneous

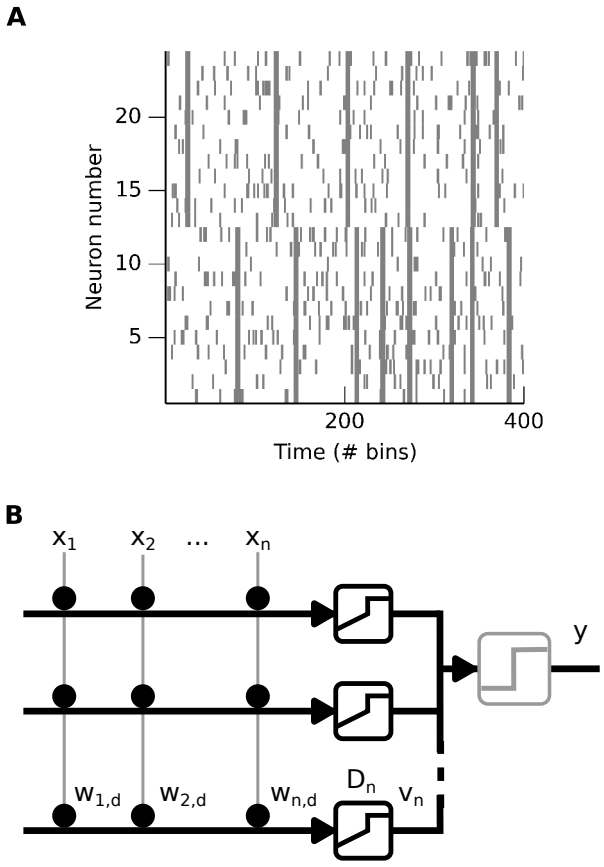

Figure 2. Presynaptic inputs and the postsynaptic neuron model. A. Raster plots of 25 presynaptic inputs. Two distinct populations of inputs independently fire synchronous bursts of 4 consecutive spikes (indistinguishable, they look like a single event). **B**. A multi-subunits binary neuron model. It receives the n presynaptic binary inputs x (active/inactive) and models the post-synaptic neuron's binary response y (spike/no spike). It has d distinct dendritic subunits. For each time bin, each subunit independently sums their pre-synaptic inputs using a set of synaptic weights $w_{i,j}$. The synaptic architecture of the model is the entire set of synaptic weights. Non-linear dendritic functions filter these sums (black squares: D_i), and their outputs sum linearly at the soma producing or not an action potential reported by y.

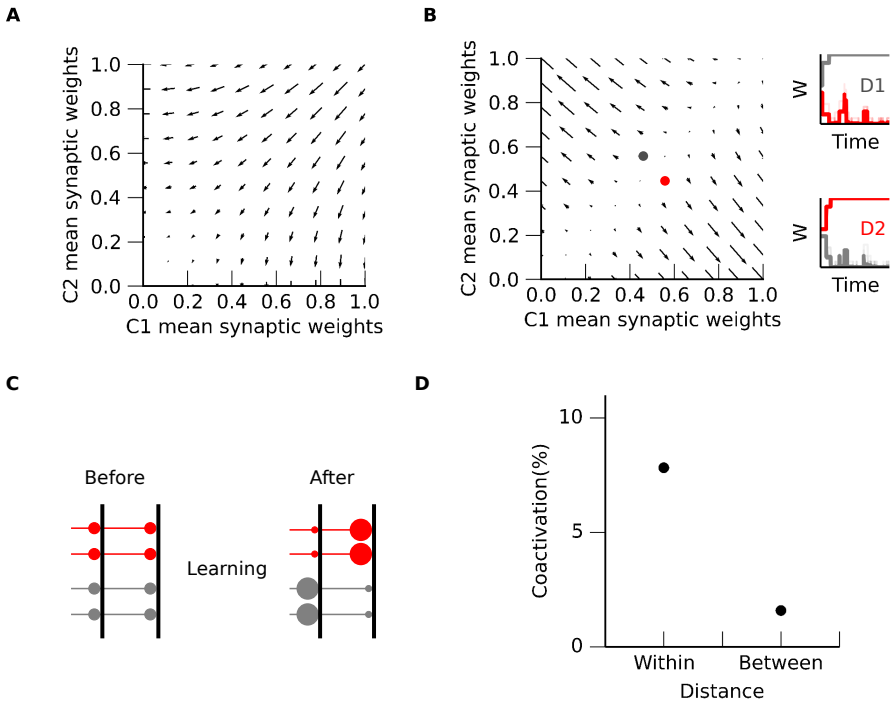

Figure 3. A learned synaptic architecture that displays synaptic clustering. **A**. A flow diagram obtained analytically for homogeneous Poisson inputs. Each arrow points toward the most likely evolution of the mean synaptic weights from C1 or C2 (populations of presynaptic inputs) given its current value. The length of an arrow is proportional to the change likelihood. **B**. In this case the Poisson process is inhomogeneous, and synchronous events occur in each population (60 synchronous event per population). The two dots correspond to two initial weight distributions. Insets are the evolution of these initial mean weights depending on the population (red/gray). **C**. The synaptic weights before (left) and after (right) learning. The size of the circles denotes the synaptic strength. **D**. C-oactivation probabilities obtained from simulations. Within/Between are probabilities of two active inputs with synaptic weights above 0.5 within/between two subunits. These simulations reproduce the observation of Kleindeinst et al 2011 [10] (n=100 repetitions starting from uniformly distributed weights).

activity, i.e. under the same inputs that were used for learning (see Materials and Methods). Consistent with the experimental result of Kleindienst et al [10], the synapses within the same dendritic branch tend to be co-active, whereas the synapses between dendritic branch tend to be active at different time points (see Fig. 3D).

The same learned synaptic architecture can also lead to synaptic scattering. In the previous section, we demonstrated that during spontaneous activity correlated groups of neurons can potentiate nearby synapses, i.e. target the same dendritic subunit (Fig 3C). We showed that this synaptic architecture displays synaptic clustering in spontaneous activity (Fig 3D, also displayed in Fig. 4A left). In this section we show that the learned synaptic architecture can also display synaptic scattering when inputs contain events deviating for the one experienced previously.

To that end, we hypothesized that evoked activity corresponds to inputs that have a different correlation structure than during spontaneous activity. In Fig. 4A, groups of inputs 1&2 and 3&4 were correlated by sharing synchronous events during spontaneous activity. On the other hand, during evoked activity, the groups of inputs 1&3 and 2&4 were correlated. During evoked activity, the neuron exhibits synaptic scattering, as shown in (Fig. 4A right). For synaptic clustering to happen during spontaneous activity, whereas synaptic scattering is seen under evoked activity, the neuronal and subunits threshold need to be set appropriately, as seen on Fig. 4A: one group of active inputs is enough to activate a subunit, but the two subunits need to be activated to make the neuron fire, as observed experimentally [23].

In Fig. 4A, for evoked activity, we chose totally different correlated groups than those for spontaneous activity (1&2, 3&4 versus 1&3, 2&4). We were interested in understanding how different evoked activity has to be from spontaneous activity to ensure synaptic scattering and that the neuron spikes. To test that, we probe our model with different spontaneous activity: if identical to spontaneous activity, the Hamming distance is 0, if completely orthogonal, the Hamming distance is 10, since we simulated 20 correlated input with 4 dendritic subunits (Fig. 4B). If inputs are identical to spontaneous activity (inputs that were used to train the neuron), the neuron stays silent, but when the Hamming distance is higher than 6, the neuron expresses synaptic scattering, and therefore activate enough dendritic subunits to make the neuron spike. To summarise, the neuron stays silent to the statistics of inputs it was trained for and fires for unexpected or novel stimuli, leading to sparse activity.

Learning can lead to hyper-excitability with pathologically low number of dendrites. We just demonstrated that our learning mechanism can lead to interesting computations, when the number of dendritic subunits is sufficiently high. But the same learning mechanism can lead to a maladaptive behaviour, that is, hyper-excitability, when the number of subunits diminishes. For example, if the neuron only has two dendritic subunits, then learning can lead to two likely situations as shown in Fig. 5A: We denote the first situation normal because each group contacts a distinct dendritic subunit, and the second situation pathological because a single group is contacting both dendritic subunits. These two situations are equally likely when the model has two subunits, but this probability steeply decreases as the number of subunits increases. With a large number of dendrites, it is unlikely that a single group of neuron targets all dendritic subunits. In fact, the probability of a normal situation exponentially increases with the number of dendritic subunits.

Fig. 5B demonstrates that in a normal situation, the firing rate of the postsynaptic neuron remains low during learning. In a situation with 8 subunits the pathological situation arises in less than 10 cases out of a 100. When the number of dendritic subunits drops to 2 ,the postsynaptic neuron fire abnormally high at the end of learning in 50% of the cases. This high firing rate is associated with the pathological condition, where the same group of correlated neurons makes strong synaptic connections on all

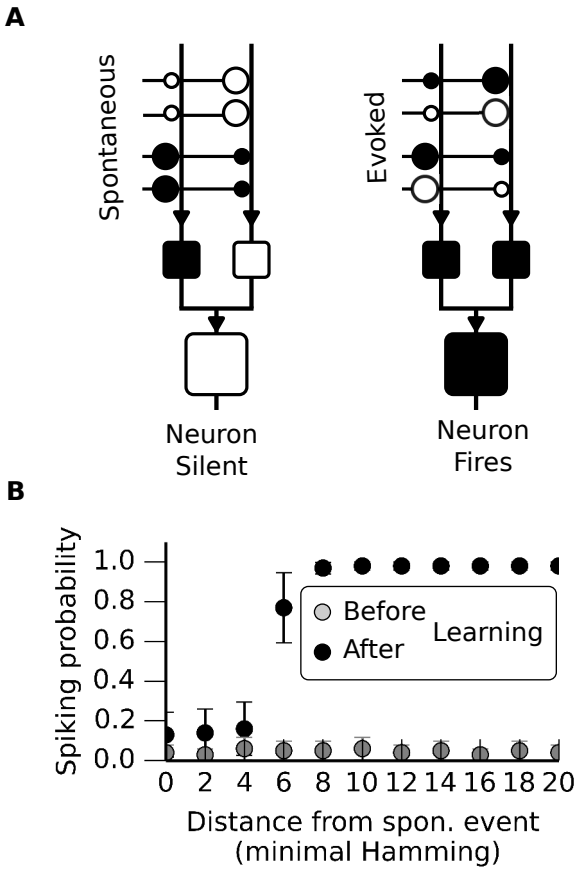

Figure 4. The same synaptic architecture can display synaptic scattering. **A**. A neuron was trained under spontaneous activity. The size of the circle shows the synaptic strength, after learning. After learning, the neuron under spontaneous activity shows synaptic clustering (left - two big black circles on the same dendritic branch) and synaptic scattering under evoked activity (right - two big black circles on different dendritic branch). Each synapses (circles), subunits (small squares) and neuronal output (big square) are black is active and white if in-active. **B**. The probability of spiking given the minimal Hamming distance between a evoked activity and spontaneous activity, which was used to train the neuron. Note that a Hamming distance of 0 means that the evoked activity is the same as spontaneous, and a distance of 20 means that evoked activity is as different as possible from spontaneous activity.

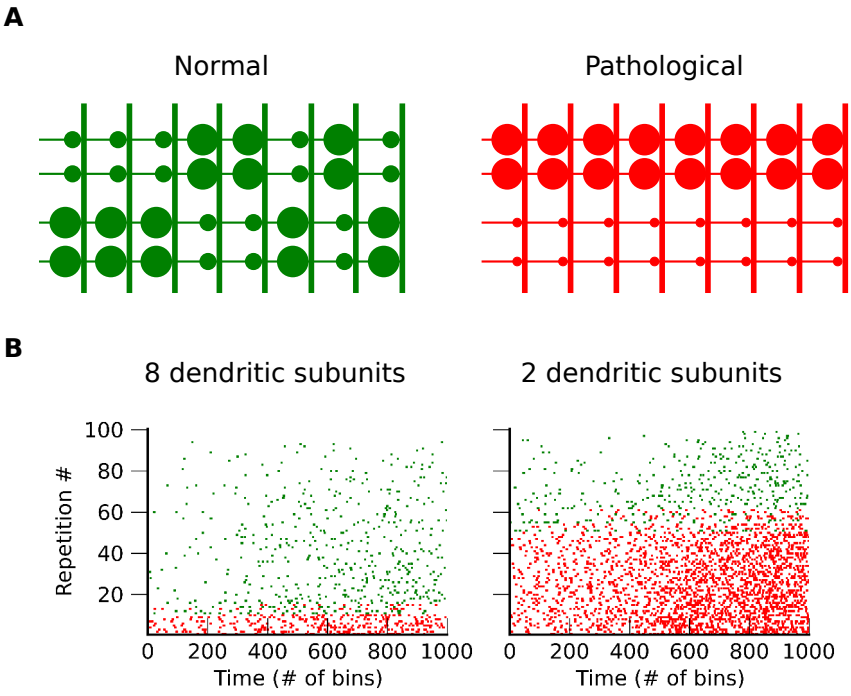

Figure 5. Pathological activity arises from reduced dendritic morphology. **A**. Schematic depiction of the normal (green) and the pathological case (red). Circles are synaptic weights, their diameter is proportional to their strength. In the pathological case, the same population of correlated neurons forms synapses on all dendritic subunits. **B**. Raster plot of the postsynaptic activity for hundred repetitions during learning. For a sufficient number of dendritic subunits, learning leads to low rates (green). However, as the number of dendritic subunits decreases (from 8 to 2 subunits), the neuron becomes hypersensitive to presynaptic activity, and fires at pathologically high rates (red). Note that the color of the spike trains are set so that it reflects the synaptic architecture (as shown in A).

dendritic subunits (red). In such a situation any active neuron from this group will make the postsynaptic neuron fire. Importantly, the adaptive property associated with synaptic scattering disappears in the pathological condition and only the hyper-excitability remains. This last results is interesting in light of several diseases associated with a reduction in dendritic branching. For example, in Alzheimer's disease [19], dendrites are reduced and hyper-excitability is observed.

Discussion

We introduced a multi-subunit binary neuron model with a single synaptic architecture capable of exhibiting both synaptic clustering and scattering: during spontaneous activity, the neuron shows synaptic clustering, whereas during evoked activity, we observe synaptic scattering. The neuron showed selectivity to sensory evoked episodes diverging from spontaneous activity. Finally, we demonstrated how the same learning mechanism can lead to hyper-excitability as the number of dendritic subunits diminishes a phenomenon observed in a syndrome like Alzheimer's disease [19].

Mel et al. [6] predicted the existence of synaptic clustering because of dendritic non-linearities. Many studies have already suggested possible roles for nonlinear dendrites in which synaptic clustering is observed [4, 24, 25]. Interestingly, our results show that dendritic non-linearities can also enhance single neuron computation when synaptic scattering is observed. Nonlinear dendrites allow our model, which displays synaptic scattering, to learn a linearly non-separable input-output mapping, unreachable for a single compartment model [2, 26]. Moreover, we demonstrate here that synaptic scattering leads to sparsification of the input signal: since learning is sensitive to the statistics of synchronous events, the neuron learns to stay silent for events consistent with the input statistics during learning, and to fire only for events deviating from it. This leads to novelty-detection, a well-known problem in statistical learning [27], which we show here can be performed with as little as a single neuron.

Another strength of this work is to reconcile two bodies of experimental observations. Synaptic clustering and scattering are not mutually exclusive, but can co-exist, depending on the absence/presence of sensory stimulation. Our result also makes further experimental predictions. For instance, we predict that synaptic activity might cluster during sleep, but scatter during periods of activity, i.e. in the awake brain. This could be tested by monitoring dendritic spine calcium signals of neocortical pyramidal neurons in different brain states or level of anesthesia. Our study also provides a mechanistic explanation for linear summation during sensory-evoked activity [14], and an explanation for why multiple branches are necessary to make a pyramidal neuron spikes [28].

In conclusion, our theoretical study has sewn together several patches of experimental observations, unifying synaptic clustering and scattering into a coherent whole. We have further shown how learning can unlock the computational advantages of nonlinear dendrites. Finally we have proposed a possible explanation for the correlation between dendritic shrinkage and the neuronal hyper-excitability observed in mouse models of Alzheimer's Disease.

Materials and Methods

Inputs and Output. To model synaptic inputs we used an inhomogeneous Bernouilly process. In each time bin, the probability of firing $x_i = 1$ is either 0.01 or 1 (during a synchronous event). These inputs are then integrated by the postsynaptic neuron resulting in a binary output y. Synaptic integration has two steps in a multi-subunits

binary neuron model. Firstly, the set of binary inputs $x_1, x_2, \ldots, x_n$ sum linearly in each subunit $D_1, D_2, \ldots, D_d$ given a local set of weights. It results in a local signal $v_i = \sum_j D_i(w_{i,j}x_{i,j})$ with D a function with a threshold θ at which a jump of d is made and where v stops to increase. Secondly, all the resulting v are linearly summed at the soma which fires or not $y = S\big(\sum_i v_i\big)$. Here S is a Heaviside functions with threshold Θ. To make the neuron scatter sensitive, we set the dendritic threshold equal to the correlated neuron group size and the somatic threshold just above the saturation value of a single subunit.

Co-activation probability. To compute the co-activation probability we first thresholded all synaptic weights w to determine if a synaptic contact was made. We arbitrarily set this threshold to 0.5. We then take the set of inputs played during learning and we computed the co-activation probability between every pair of inputs which formed a synaptic contact. For instance if x_1 and x_2 both form a synaptic contact on the subunit i, the coactivation probability of $w_{1,i}$ and $w_{2,i}$ equals $p(x_1 = 1 \vee x_2 = 1)$.

Normal / Pathological learning. In Fig. 5 we colored the output spike depending on the synaptic architecture. If the same group of correlated neuron makes synaptic contacts on all dendritic subunits the color of the spike train is red (pathological) otherwise it is blue (normal).

We used Python v2.7, Numpy v1.3 and Matplotlib v1.4.0 to code, process and display the result of all our simulations. This code is available on a git repository (link to be supplied for publication).

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