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Neuronal-Based Synaptic Compensation: A Computational Study in Alzheimer's Disease

David Horn
Nir Levy
School of Physics and Astronomy,
Raymond and Beverly Sackler Faculty of Exact Sciences,
Tel-Aviv University, Tel Aviv 69978, Israel

Eytan Ruppin
Departments of Computer Science and Physiology,
Tel-Aviv University, Tel Aviv 69978, Israel

In the framework of an associative memory model, we study the interplay between synaptic deletion and compensation, and memory deterioration, a clinical hallmark of Alzheimer's disease. Our study is motivated by experimental evidence that there are regulatory mechanisms that take part in the homeostasis of neuronal activity and act on the *neuronal* level. We show that following synaptic deletion, synaptic compensation can be carried out efficiently by a *local, dynamic* mechanism, where each neuron maintains the profile of its incoming postsynaptic current. Our results open up the possibility that the primary factor in the pathogenesis of cognitive deficiencies in Alzheimer's disease (AD) is the failure of local neuronal regulatory mechanisms. Allowing for neuronal death, we observe two pathological routes in AD, leading to different correlations between the levels of structural damage and functional decline.

1 Introduction

Alzheimer's disease (AD) is characterized by progressive deterioration of the patient's cognitive and social capabilities. Recent investigations have shown that in addition to the traditionally described plaques and tangles found in the AD brain, this disease is characterized by considerable synaptic pathology. There is significant synaptic loss in various cortical regions, termed *synaptic deletion*, accompanied by *synaptic compensation*, an increase of the synaptic size reflecting a functional compensatory increase of synaptic efficacy (Bertoni-Freddari *et al.* 1990; DeKosky and Scheff 1990; Scheff *et al.* 1993). The combined outcome of these counteracting synaptic degenerative and compensatory processes can be evaluated by measuring the total synaptic area per unit volume (TSA),

which is initially preserved but decreases as the disease progresses. The TSA has been shown to strongly correlate with the cognitive function of AD patients (DeKosky and Scheff 1990; Terry *et al.* 1991; Masliah *et al.* 1994; Masliah and Terry 1994), pointing to the important role that pathological synaptic changes play in the cognitive deterioration of AD patients. In this paper, we further develop our previous studies of the functional effects of these synaptic changes, and discuss their relation to more traditional neuropathological markers of AD.

Since memory deterioration is a clinical hallmark of AD, it is natural to investigate the effects of synaptic deletion and compensation on the performance of an associative memory neural model. Motivated by the findings of synaptic pathology in AD, we previously studied (Horn *et al.* 1993; Ruppin and Reggia 1995) ways of modifying the remaining synapses of an associative memory network undergoing synaptic deletion, such that its performance will be maintained as much as possible. To this end, we used a biologically motivated variant of a Hopfield-like attractor neural network (Tsodyks and Feigel'man 1988): M memory patterns are stored in an N-neuron network via a Hebbian synaptic matrix, forming fixed points of the network dynamics. The synaptic efficacy J_{ij} between the jth (presynaptic) neuron and the ith (postsynaptic) neuron in this network is

$$J_{ij} = \frac{1}{N}\sum_{\mu=1}^{N}(\eta^{\mu}{}_{i} - p)(\eta^{\mu}{}_{j} - p) \tag{1.1}$$

where $\eta^{\mu}{}_{i}$ are (0,1) binary variables representing the stored memories and p is the activity level of each memory. The updating rule for the state V_i of the ith neuron is given by

$$V_i(t+1) = \Theta\left[\sum_{j\neq i}^{N} J_{ij}V_j(t) - T\right] \tag{1.2}$$

where Θ is the step function and T, the threshold, is set to its optimal value $T = \frac{1}{2}p(1-p)(1-2p)$. In the intact network, when memory retrieval is modeled by presenting an input cue that is sufficiently similar to one of the memory patterns, the network flows to a stable state identical with that memory. Performance of the network is defined by the average recall of all memories. The latter is measured by the *overlap* m^{μ}, which denotes the similarity between the final state V the network converges to and the memory pattern η^{μ} that is cued in each trial (see Horn *et al.* 1993).

Synaptic deletion has been carried out by randomly removing a fraction d of all synaptic weights, such that a fraction $w = 1 - d$ of the synapses remains. *Synaptic compensation* was modeled by multiplying all remaining synaptic weights by a common factor c. Varying c as a function of d specifies a compensation strategy. Correlating synaptic size with synaptic strength, we have interpreted TSA in the model as proportional to $c \cdot w$. In this framework we have previously shown that maintaining

the premorbid levels of TSA (that is, employing $c = 1/w$) constitutes an optimal compensation strategy, which maximally preserves performance as synapses are deleted. However, such uniform, global strategies suffer from two fundamental drawbacks:

1. They can work only when neurons in the network undergo a similar, uniform, process of synaptic deletion. Otherwise, it is advantageous for the different neurons, which undergo different levels of synaptic deletion, to develop their own suitable compensation factors.
2. While global compensation mechanisms may be carried out in biological networks via the actions of neuromodulators, their biological realization remains problematic, since it requires the *explicit* knowledge of the ongoing level of synaptic deletion in the whole network.

In this paper we present a solution to these problems by showing that synaptic compensation can be performed successfully by *local* mechanisms: a fraction d_i of the input synapses to each neuron i is deleted, and is compensated for by a factor c_i that 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 $w_i = 1 - d_i = \sum_j w_{ij}/N$. Our method is based on the neuron's post-synaptic potential h_i, and does not require the explicit knowledge of either global or local levels of synaptic deletion. The local compensatory factor c_i develops dynamically so as to keep the membrane potential and neural activity at their original, premorbid levels. The proposed *neuronal* activity-dependent compensation modifies all the synapses of the neuron concomitantly, in a similar manner, and thus differs fundamentally from conventional Hebbian *synaptic* activity-dependent modification paradigms like long-term potentiation and long-term depression, which modify each synapse individually. Our proposal is that while synaptic activity-dependent modification plays a central role in memory storage and learning, neuronal-level synaptic modifications serve to maintain the functional integrity of memory retrieval in the network.

Several biological mechanisms may take part in neural-level synaptic modifications that self-regulate neuronal activity (see van Ooyen 1994 for an extensive review). These include receptor up-regulation and down-regulation (Turrigiano *et al.* 1994), activity-dependent regulation of membranal ion channels (Armstrong and Montminy 1993; Abbott *et al.* 1994), and activity-dependent structural changes that reversibly enhance or suppress neuritic outgrowth (Mattson and Kater 1989; Schilling *et al.* 1991; Grumbacher-Reinert and Nicholls 1992). Interestingly, while neurotransmitters' application may act in isolation on individual dendrites, membrane depolarization simultaneously regulates the size of all growth cones and neurites of a given neuron (Stuart and Sakmann 1994). Taken together, these findings testify that there exist feedback mechanisms that act on the neuronal level, possibly via the expression of immediate early

genes (Morgan and Curran 1991), to ensure the homeostasis of neuronal activity. These mechanisms act on a slow time scale and are active also in the normal adult brain. These biological data have recently triggered the computational study of feedback regulation of neuronal dynamics (Abbott and LeMasson 1993; LeMasson *et al.* 1993), and activity-dependent network development (van Ooyen and van Pelt 1994).

In this paper, we extend the study of neuronal activity regulation to investigate the role of local compensation mechanisms in the pathogenesis of AD. We raise the possibility that synaptic compensatory mechanisms, that in normal aging succeed in preserving a considerable level of cognitive functioning, are disrupted in AD. To study this further, we concentrate on synaptic weight modification, where each weight is taken to represent the functional efficacy of the synapse, i.e., its size and the activity of related receptors and ion channels.[1] In the next section, we present local compensation algorithms in two classes of associative memory models. First, in the framework of the Tsodyks-Feigel'man (TF) model where we have previously studied global strategies, and then in the framework of the Willshaw model (Willshaw *et al.* 1969). These models are representatives of two fundamentally different classes of associative networks, differing in the characteristics of the neurons' mean postsynaptic potential and the level of competitiveness in the network. This distinction has important biological ramifications, but as the pertaining experimental data are currently insufficient to decide which class is biologically more plausible, we study local synaptic compensation in both frameworks. Computer simulations, and their possible clinical implications, are presented in Section 3. The synaptic changes are obviously only part of a complex and interrelated set of neuropathological changes that take place in AD. In Section 4 we briefly discuss these alterations and their relations to the synaptic processes we model. Finally, in the last section we summarize our results and their relevance to understanding the pathogenesis and progression of Alzheimer's disease.

2 Locally-driven Synaptic Compensation

2.1 The Tsodyks Feigel'man Model. Our local compensation method aims at maintaining the premorbid profile of the postsynaptic potential. In our previous work (Horn *et al.* 1993) it was shown that this profile can be maintained through *TSA conservation*, i.e., by using the compensation $c = 1/w$. Guided by this finding, we now set to implement its local compensation version, $c_i = 1/w_i$. For this purpose we employ the differential equation

$$\frac{dc_i}{dt} = \kappa c_i (1 - \hat{w}_i c_i) \tag{2.1}$$

[1] From a strict computational point of view, the synaptic modifications we study are equivalent to variations in the firing threshold of each neuron.

where κ is a rate parameter and $\hat{w}_i$ is a *field-dependent* estimate of the local connectivity w_i. This equation is then transformed to a difference equation, which is used in the simulations

$$c_i(t + \Delta t) = c_i(t) + \tau c_i(t)\,[1 - \hat{w}_i c_i(t)] \tag{2.2}$$

where $\tau = \kappa \Delta t$.

We are looking for an estimate $\hat{w}_i$ that depends only on information that is available to the single neuron. We propose using moments of the neuronal input field (postsynaptic potential) h_i, after averaging over a set of retrieval trials, and comparing them with their values in the normal, premorbid state. From a biological perspective, such knowledge and computational algorithms may be prewired in the neuronal regulatory mechanisms reviewed in the previous section, which are responsible for homeostasis of neural activity.

There are two possible measurements of the field h_i, either under conditions of random noise input or through a set of trials of memory retrieval from the existing repertoire of memories.[2] In the Tsodyks-Feigel'man model, the first moment of the field vanishes, $\langle h_i \rangle = 0$, both for random inputs and memories. So we turn to the second moment, which can be calculated for random noise initial conditions in the premorbid state

$$\left\langle h_i^2(w_i) \right\rangle = c_i^2 \hat{w}_i \left\langle h_i^2(w_i = 1) \right\rangle \equiv c_i^2 \hat{w}_i \left\langle R_i^2 \right\rangle \tag{2.3}$$

When using a set of memories instead of random noise we obtain a different expression that separates into signal and noise terms with different power dependence on deletion

$$\left\langle h_i^2(w_i) \right\rangle = c_i^2 \hat{w}_i^2 \left\langle S_i^2 \right\rangle + c_i^2 \hat{w}_i \left\langle R_i^2 \right\rangle \tag{2.4}$$

Here $\langle S_i^2 \rangle$ is the signal term in the premorbid state ($w = 1$) and $\langle R_i^2 \rangle$ is the same noise term as in 2.3. Given these two equations one can solve for $\hat{w}_i$ either by using noise alone, or by using trials of memory retrieval and relying on the separate knowledge of the premorbid magnitude of the signal and noise terms.

To perform local synaptic compensation in our simulations, we proceed in small steps of deletion Δd. At each deletion step the network is presented with all (slightly corrupted) memories and allowed to converge to its fixed points. By averaging the field strengths measured over all memory retrieval trials, we calculate $\hat{w}_i$ via equation 2.4. Thereafter, synaptic compensation via algorithm 2.2 is applied. The resulting performance is evaluated by presenting all memory cues again. As demonstrated in Figure 1, dynamic local compensation via algorithm 2.4 works as well as or even better than the local TSA-conserving compensation $c_i = 1/w_i$.

[2]One may speculate that the biological realization of such field measurements occurs during dreaming.

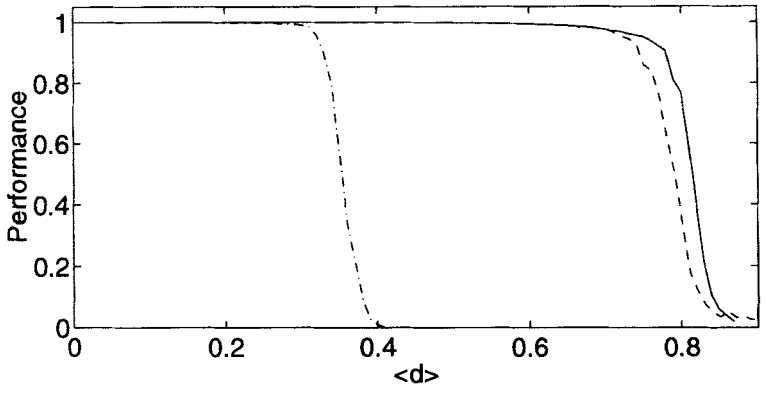

Figure 1: Performance versus deletion for a network that runs the local TF-compensation algorithm via 2.2 and 2.4. The result, presented by a solid line, is compared with the performance of local TSA conserving method ($c_i = 1/w_i$, dashed curve) and no compensation ($c_i = 1$, dot-dashed curve). The simulation parameters were $N = 1000, M = 100, p = 0.1, \tau = 0.25, \Delta d = 0.01$.

2.2 The Willshaw Model. A simpler, and perhaps more biologically plausible mechanism of local synaptic compensation arises in the Willshaw model (Willshaw *et al.* 1969), where memory patterns are stored in excitatory synapses through the rule

$$J_{ij} = \frac{1}{Np}\Theta\left(\sum_{\mu=1}^{M} \eta^{\mu}_{i}\eta^{\mu}_{j}\right) \tag{2.5}$$

The updating rule is similar to equation 1.2 and each neuron has a uniform threshold T smaller than 1. In the Willshaw model, unlike the TF model, spurious states with high activity emerge as deletion proceeds. These deviations of the Willshaw network activity level from its premorbid values rule out the possibility of accurately estimating the connectivity w in a manner analogous to the way equations 2.3 and 2.4 were used in the TF model. However, in the Willshaw model $\langle h_i \rangle \neq 0$ so instead of estimating the connectivity from moments of the field and using it for the compensation algorithm as in equation 2.1, we can now use the changes in the field itself to correct for the effects of synaptic deletion directly,

$$\frac{dc_i}{dt} = \kappa c_i \left[1 - \frac{\langle h_i(t)\rangle}{\langle h_i(t=0)\rangle}\right] \tag{2.6}$$

When the dynamics remain similar to those of the intact network, this method is close to the TSA-conserving strategy ($c_i = 1/w_i$). However,

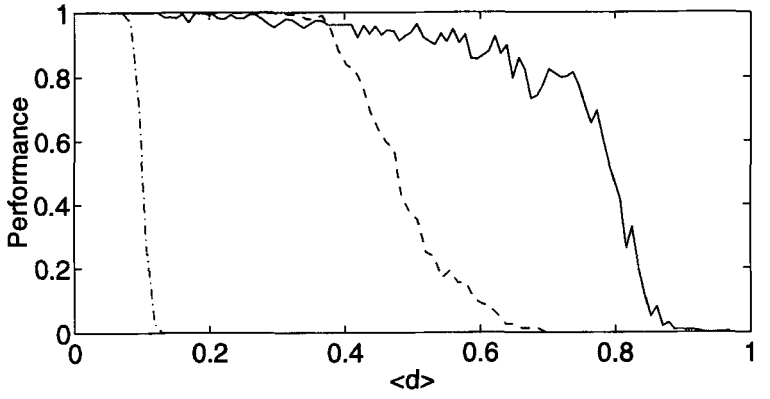

Figure 2: Performance versus deletion for a network that runs the local Willshaw-compensation algorithm 2.6. The result, presented by a solid line, is compared with the performance of local TSA conservation ($c_i = 1/w_i$, dashed curve) and no compensation ($c_i = 1$, dot-dashed curve) methods. The simulation parameters were $N = 1500, M = 75, p = 0.05, \tau = 0.1, \Delta d = 0.009$.

as demonstrated in Figure 2, the new, direct, field-dependent method (the discretized version of equation 2.6) is markedly superior to the TSA-conserving strategy ($c_i = 1/w_i$) as changes in the level of activity of the network occur; the high-activity spurious stable states that emerge as deletion proceeds are suppressed by using compensation values that are lesser than those dictated by a TSA-conserving algorithm (which is of course insensitive to the level of activity in the network), resulting in better performance.

This simple and efficient algorithm is used in the next section to study the effect of synaptic deletion and compensation rates on network performance, and its relevance to AD progression.

3 Results and Clinical Relevance

3.1 Compensation Rates and AD Progression. In this section we will discuss results of simulations of a Willshaw network of $N = 1500$ neurons in which $M = 75$ randomly generated memory patterns with activity $p = 0.05$ are stored with $T = 0.8$. In every simulation run, a sequence of synaptic deletion and compensation steps is executed, and the performance of the network is traced as deletion progresses. In each simulation step (considered as one time unit) a fraction Δd of the remaining synapses is deleted. Synaptic compensation is performed via the dis-

cretized version of algorithm 2.6 by averaging the local field following the presentation of the stored memories.

We first study the network's performance at various compensation rates τ, as presented in Figure 3a. The performance level is better maintained if the compensation rate is high. As reviewed in Horn *et al.* (1993), young and very old AD patients suffer from rapid clinical deterioration characterized by a sharp decline, 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 (that is, corresponding to low compensation rates illustrated in the leftmost curve in Fig. 3a), and young patients still have potent synaptic compensation mechanisms (the rightmost curve). Interestingly, studies of reactive synaptogenesis following experimental hippocampal deafferentation lesions in rodents show indeed that the *rate* of compensatory synaptogenesis decreases as a function of age (Cotman and Anderson 1988, 1989). The dependence of performance on compensation rate τ for a given deletion level d is demonstrated in Figure 3b; while the performance levels obtained in early stages ($d = 0.4$) are almost similar for a broad range of τ values, a more pronounced τ dependence is observed as deletion proceeds ($d = 0.8$).

To examine how the rate of synaptic deletion affects performance, we kept the compensation rate τ constant and varied Δd. The results are basically similar to the results displayed in Figure 3a; the performance decreases as the rate of deletion increases. Hence, when there is a significant "mismatch" between synaptic deletion and compensation, whether its origin is increased synaptic deletion or decreased compensation rates, the network's performance degrades. In the intermediate range, the network's performance degrades in a fairly gradual manner. Thus, when local compensation is employed, a single compensation mechanism can give rise to a variety of clinically observed patterns of degradation.

3.2 Memory Vacillations. Similar simulations performed within the framework of the TF model yield qualitatively similar results. However, there are two important differences: First, in the TF model performance degradation is homogeneous, that is, all memories have similar retrieval acuity. In the Willshaw model, the retrieval of some memories may decline while others are preserved. Furthermore, while in the TF model once a memory pattern vanishes it is lost forever, in the Willshaw model memory patterns that are lost may later be adequately retrieved due to ongoing compensation. Figure 4 traces the temporal evolution of individual overlaps of four memory patterns in a Willshaw network during deletion and compensation. While some patterns may vanish forever (left uppermost figure), the retrieval of others may vacillate (right uppermost and left lower figures), and some may even have late revival (right lowermost figure). These results demonstrate that computational studies of brain pathologies may potentially enable us to learn more about the

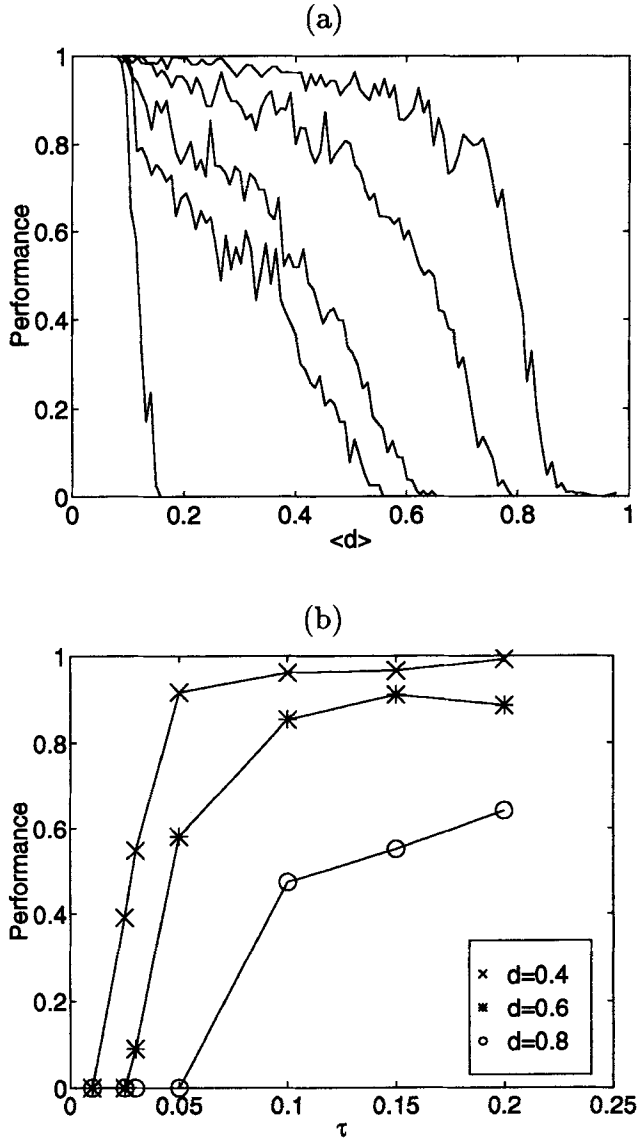

Figure 3: (a) Performance versus deletion for different compensation rates. τ is increased from left to right, with values $0.01, 0.025, 0.03, 0.05, 0.1$. $\Delta d = 0.009$. (b) Performance versus τ for fixed d values.

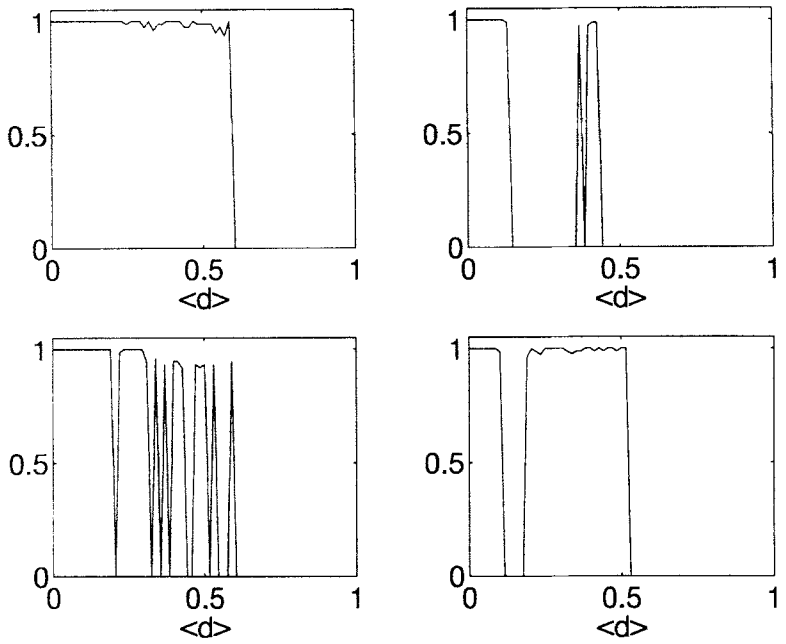

Figure 4: Overlaps of individual patterns. The simulation parameters were $\Delta d = 0.015$ and $\tau = 0.05$.

working of the intact brain; in this example, the TF model and the Willshaw model give rise to inherently different patterns of individual memory decline as AD (and normal aging) progresses. A detailed prospective psychological study of individual long-term memory retrieval is called for.[3]

3.3 Two Routes to Dementia. The pathological synaptic changes in Alzheimer's disease are accompanied by the eventual loss of about 10–20% of cortical neurons (Katzman 1986; Masliah 1995). Motivated by developmental studies showing death of hypoactive neurons [see van Ooyen (1994) for a review], and the assumed degeneration of hypoac-

[3] An intuitive insight into the different behaviors of the TF and Willshaw models may be obtained by noting that in the Willshaw model all foreground neurons belonging to a given memory (those that should fire) have similar input fields, and hence tend to be activated together. In the TF model, on the other hand, the distribution of input fields of such foreground neurons is broad, hence memory patterns can still be partially retrieved even if some foreground neurons become quiescent.

tive neurons in AD (Bowen *et al.* 1994), we incorporate a neuronal degeneration rule that kills neurons as their input field decreases below a *viability-threshold (VT)* value. In addition we set upper bounds on the neuronal compensation factors. Both viability thresholds and compensation bounds may vary within certain limits over the neural population. Figure 5a and b illustrates the differential effect of high versus low neuronal viability thresholds: Obviously, different viability thresholds lead to distinct resiliency of the network to damage. But more interesting, they also give rise to different relations between the level of neuronal death and network performance. In general, there are two principal pathological pathways in which performance collapses in the network as deletion proceeds:

1. *Synaptic loss*, i.e., a strong decrease in the synapse/neuron ratio. This requires low viability thresholds, and may lead to large cognitive deficits with little structural damage.
2. *Neuronal loss*, which is expected to occur for higher values of viability thresholds. This will generally cause a faster avalanche of the disease, once it starts to take place, and significant neural death. A qualitatively similar effect may be seen with low versus high compensation rates.

Since the primary factor responsible for cortical atrophy in AD is likely to be neural degeneration [synapses occupy a very small fraction of the cortical volume (Bourgeois and Rakic 1993)], the finding that the extent of neural damage depends on the pathological pathway may shed some light on the broad range of cortical atrophy levels observed in AD patients, suffering from similar levels of cognitive deterioration (Wippold *et al* 1991; Murphy *et al.* 1993).

4 Plaques, Tangles, and Synaptic Pathology

In addition to the neurodegeneration of the association and limbic cortices, the two main neuropathological alterations that accompany the progression of AD are neuritic plaques (composed mainly of degenerating neurites and amyloid) and neurofibrillary tangles (composed mainly of microtubule associated tau protein) (Terry *et al.* 1994). Recent experimental observations offer new insights regarding the relationship between plaques and tangles and synaptic alterations in AD:

- Amyloid plaques: The extracellular deposition of amyloidogenic plaques is likely to play an important role in neural and synaptic degeneration [see Masliah and Terry (1994) and Masliah (1995) for a review]. However, the existence of widespread neuritic dystrophy that is not directly associated with amyloid deposits (Selkoe 1994), and the observation that plaque and tangle formation can account only partially for synaptic pathology, suggest that there is an additional, primary, synaptic pathogenic process in AD (Masliah and Terry 1994; Masliah 1995). This process may result from the

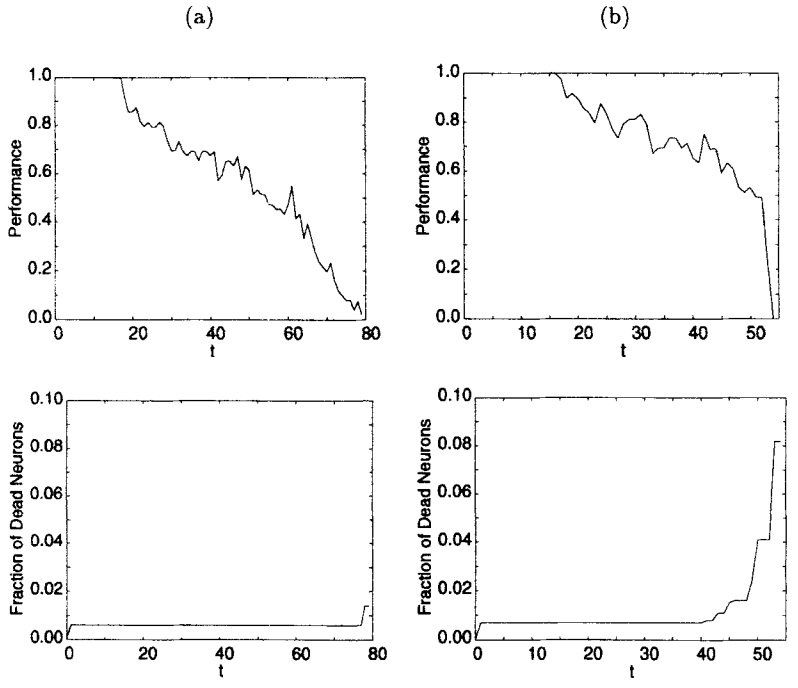

Figure 5: Performance versus time with (a) a low viability threshold ($VT = 0.2$) and (b) a high viability threshold ($VT = 0.5$). $\tau = 0.02$ and the rest of the simulation parameters are as in Figure 4. The bottom figures trace the fraction of dead neurons as a function of time. Neuronal damage is traced until complete performance collapse (the patient's "death"), i.e., zero overlap.

dysfunction of several synaptic proteins, including impaired amyloid precursor protein (Roch *et al.* 1994; Masliah 1995). It remains to be determined if these synaptic regulation abnormalities manifest themselves primarily in enhanced synaptic degeneration or in attenuated rates of synaptic regeneration and compensation.

- Tangles: The main common underlying pathology for a wide variety of neuropil abnormalities in AD is the accumulation of the microtubule-associated protein Tau in neurofibrillary tangles (Perry *et al.* 1991; McKee *et al.* 1991). Neuronal-level synaptic compensation, involving early gene expression and protein transcription, probably requires intact cellular transport systems. Hence, disrupted microtubule systems may lead to deficient synaptic com-

pensation. While neurofibrillary pathology is likely to contribute to dementia in AD (Arrigada *et al.* 1992; Samuel *et al.* 1994), there is a subgroup of AD patients that shows little neurofibrillary pathology and yet may suffer from considerable cognitive deterioration (Terry *et al.* 1987). If indeed damaged synaptic compensation arises from neurofibrillary pathology, then the dementia in these no-tangles subgroups is predicted to arise primarily from excessive synaptic pruning (i.e., markedly reduced synaptic density, which may be observed in morphometric studies) in face of maintained TSA (which can be measured both by morphometric and immunohistochemical techniques).

- Plaques and tangles may not only cause synaptic pathology, but, in turn, synaptic alterations may enhance plaque and tangle formation, yielding a "vicious cycle" of neural damage and death; abberant "compensatory" synaptic sprouting may enhance neuro degeneration (Masiliah *et al.* 1991; Cotman *et al.* 1991) and plaque formation (Masliah *et al.* 1992). The functional effects of sprouting on network performance are important and interesting topics for future computational studies; interestingly, previous investigations in associative neural models have shown that increased synaptic noise may have beneficial as well as adverse effects (Horn and Ruppin 1995).

In summary, synaptic pathology may either be a direct result of an underlying molecular defect affecting synapses, or a secondary result of neural loss, and plaque and tangle formation. Given the current state of knowledge of the mechanisms underlying AD pathology, this issue is an open question, and our model is still not rich enough to address it. The development of combined neural/metabolic models to study the interplay between synaptic alterations and more conventional markers of AD pathology is called for. Such models may shed further light on the relative significance of the two routes to dementia delineated in this work.

5 Summary

We have shown that synaptic compensation, a process that appears to play an important role in attenuating the progression of AD, can be achieved in a stable manner via local, activity-driven mechanisms. The biologically motivated mechanisms introduced in this paper act to maintain neuronal homeostasis. Within our model, the variation of a single parameter, the compensation rate, describes the different progression rates of cognitive deterioration observed in AD.

Our work points to the possible important role of synaptic compensation failure in the progression of Alzheimer's disease. This failure probably reflects a breakdown of regulatory mechanisms that play a part

in maintaining the functional integrity of the aging, *nondemented*, brain (Buell and Coleman 1979; Flood and Coleman 1986; Bertoni-Freddari *et al.* 1988, 1990).

We have based our compensation model on the observation of increased synapses in the aged and demented brains. Considerable support to the *functional* significance of structural synaptic compensatory changes has been furnished by electrophysiological studies in the aging rodent hippocampus [see Barnes (1994) for a review], indicating that older rats have fewer, but structurally larger and functionally stronger synapses. Recently, it was also shown that the infusion of nerve growth factor in aged rats causes a significant increase in the TSA per unit volume of cortex, which is correlated with improved cognitive performance (Chen *et al.* 1995). This gives further support to the main mechanism that we propose.

We have discussed the existence of two pathological routes of damage in AD, "synaptic" and "neural" ones. Severe cognitive deterioration may occur via either route, but the neural route leads to considerably more cortical atrophy than the synaptic route, while causing similar levels of cognitive deterioration. We hypothesize that the profile of pathological routes taken in a specific AD patient depends on the distribution of his neuronal viability thresholds.

In addition to the development of combined neural/metabolic models, our work can be extended in the future in a few directions. We have studied so far global and local synaptic compensation methods. Other intermediary synaptic compensation methods may be of interest. The utilization of higher moments of the neuron's input field may enable the realization of more efficient synaptic compensation regimes, that can counteract the pathological effects of nonuniform, *biased*, synaptic deletion. We may even envisage the possibility of using compensation algorithms as applications to the generation of "self-maintaining" associative memory network chips.

Finally we wish to reiterate the point made in the introduction: Our key idea is the existence of a *neuronal* activity-dependent compensation mechanism. This differs from Hebbian *synaptic* modification, which plays a central role in memory storage and learning. Our proposal is that neuronal-level synaptic modifications serve to maintain the functional integrity of memory retrieval in the network. Both processes are therefore needed for the proper functioning of the brain.

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