Extra-pyramidal symptoms in Alzheimer's disease: a hypothesis

– to appear in Medical Hypotheses

D. Horn
School of Physics and Astronomy,
Raymond and Beverly Sackler Faculty of Exact Sciences,
Tel Aviv University, Tel Aviv 69978, Israel

E. Ruppin
Department of Computer Science,
Raymond and Beverly Sackler Faculty of Exact Sciences,
Tel Aviv University, Tel Aviv 69978, Israel

June 30, 1992

Abstract

Recent studies have shown that compensatory processes have an important role in counteracting the neurodegenerative changes underlining Alzheimer's disease (AD), much like their well known role in Parkinson's disease (PD). In light of these reports, we review the findings of the positive correlation existing between the appearance of extra-pyramidal symptoms and an increased rate of progression in AD patients. We propose that this correlated symptomatology arises from the wasting of globally shared compensatory resources, manifested both in an increasing inability to compensate for persisting sub-clinical nigral lesions, and in enhanced AD deterioration rate. Our hypothesis gains support from various clinical reports and by the neural modeling of synaptic changes in AD.

Introduction

Recent neuroanatomical morphometric studies have found that significant synaptic changes take place in the progress of AD. A considerable decrease in the synapse to neuron ratio in AD patients due to *synaptic deletion*, has been observed [1, 2]. *Synaptic compensation*, manifested by an increase of the synaptic size, was found to take place concomittantly, reflecting a functional compensatory increase of synaptic efficacy at the initial stages of the disease [3, 2, 4]. The combined outcome of these counteracting synaptic degenerative and compensatory processes may be evaluated by measuring the total synaptic area per unit volume (TSA), which was shown to correlate with the cognitive function of AD patients

[4]. Qualitatively similar synaptic changes have been observed during normal physiological aging, but to a lesser extent [3, 2]. The compensatory increase in the number and average length of the dendritic trees' terminal segments was found to be significantly higher in nondemented aged than in AD cases [5]. In the initial stages of AD, the TSA is still maintained in some cortical layers, but as AD progresses, synaptic compensation no longer succeeds in maintaining the TSA [2, 4]. In advanced AD cases, morphological evidence of severe compensatory dysfunction have been observed [5, 6, 4].

To investigate how synaptic changes may actually determine the pattern of memory deterioration, a clinical hallmark of AD [7], we have recently used a neural network memory model incorporating synaptic deletion and compensation [8]. Uncompensated neural and synaptic deletion brings about an early collapse of the network's memory retrieval capabilities already at low levels of synaptic deletion. However, we have found that by appropriately strengthening the remaining synapses, memory performance can be preserved until the great majority of synaptic connections are deleted, when eventually performance collapses. Our results are in accordance with several post-mortem studies demonstrating that old AD patients display lesser neuropathological changes than seen in younger patients (reviewed in [9]). These findings can be accounted for by adopting the plausible assumption that older AD patients have lesser compensatory resources, and hence their disease already manifests itself clinically at earlier pathological stages. We have found that different compensation strategies lead to distinct patterns of memory deterioration, accounting for the large variability of progression rates in AD [10].

Neurodegenerative processes leading to neuronal death and synaptic deletion are known to play a major role in the pathogenesis of Parkinson's disease. The extensive loss of nigral dopaminergic projections on the striatum is accompanied by compensatory processes geared at retaining the pre-morbid dopaminergic activity [11, 12]). Initially, compensation takes place primarily via increased dopaminergic release and decreased uptake, but over time there is an increase in the responsiveness of target cells via synaptic compensation, manifested in an increase in the number of postsynaptic sites. Compensation is apparently very efficient in PD; it has been estimated that the striatal concentration of dopamine drops by 80% before symptoms appear [13]. In addition, it has been claimed that the wide disparity in the rate of progress of PD might result from individual variations in compensatory potential

among different patients [14].

Extra-pyramidal signs and increased AD progression

We have reviewed an extensive body of evidence testifying to the considerable functional capacity of compensatory processes to defer the appearance of the clinical symptomatology in AD and PD. These findings offer a new perspective for understanding the correlation between the appearance of parkinsonian-like extra-pyramidal symptoms (EP+) in AD patients, and the significantly higher rate of disease progression in these patients, compared with AD patients without EP signs (EP-) [15, 16, 17]. The EP+ patients probably did not have a concomitant Parkinson's disease, and their extra-pyramidal symptoms did not antedate the onset of AD [15]. Mayeux et al. have proposed that these patients may suffer from a more generalized form of AD, characterized by widespread degeneration of neurotransmitter systems, encompassing the nigral dopaminergic system. We propose that EP+ patients do not necessarily suffer from extensive neurodegeneration, but may suffer from a general decline in the functional capacity of compensatory mechanisms. In such a state of decompensation, a previously silent subclinical pathology of the substantia nigra may lead to the appearance of extra-pyramidal symptoms. Such subclinical nigral lesions have been claimed to be fairly common [14].

Our hypothesis provides a straightforward explanation linking the increased progression rate of AD to the presence of the extra-pyramidal signs: as testified to by the neuroanatomical studies mentioned above, during the progression of AD synaptic compensatory resources are fully exploited and wasted. Supported both by indirect clinical evidence and by neural modeling, the increasing compensatory insufficiency is claimed to lead to a rapid progression of AD. On the other hand, like most basic cellular processes, it seems plausible that synaptic compensation mechanisms are fundamentally similar throughout the brain, relying on the same resources. Hence, other systems, whose functioning relies strongly on the adequacy of synaptic compensation, may gradually dysfunction; due to the major role of compensatory processes in maintaining the functioning of the nigro-striatal system, it becomes a prime victim of such global decompensation.

There exist only few reports of degenerative changes in the substantia nigra in patients with pathologically confirmed AD [18]. A reduction in brain dopamine in AD patients has been observed, but inconsistently. Moreover, the lack of metabolic markers of high turnover

rate in the remaining neurons, possibly indicates a disturbance of compensatory mechanisms [19]. The existing data does not address the EP+ subgroup specifically, but testifies that in the general AD population the anatomical damage to the substantia nigra is fairly minor, supporting the possibility that AD patients' extra-pyramidal symptoms are caused by functional decompensation. The group of rapidly progressing AD patients included also relatively many patients suffering from psychosis [16, 17], which due to its transient nature seems to support functional decompensation rather than persistent neurodegenerative damage. This association between the occurrence of psychotic symptoms and a more rapidly deteriorating course has recently been noted again by other authors [20, 21].

Conclusions

We have claimed that AD patients with a rapidly progressing disease and extra-pyramidal symptoms are subject to a general dysfunction of the over-exploited synaptic compensatory mechanisms. Via such a scenario of general decompensation, the pace of a primary disease process is accelerated, while symptoms of a secondary disease appear concomittantly. Our hypothesis is testable by conducting a postmortem neuroanatomical study of EP+ AD patients, quantifying the extent of their neurodegenerative changes in the substantia nigra. The finding of a significantly lower level of neurodegenerative changes in these patients, versus 'regular' PD patients, would strongly support our proposal.

References

[1] Davies CA, Mann DMA, Sumpter PQ, Yates PO. A quantitative morphometric analysis of the neuronal and synaptic content of frontal and temporal cortex in patient with alzheimer's disease. *J. Neurol. Sci.*, 78:151, 1987.

[2] Bertoni-Freddari C, Fattoretti P, Casoli T, Meier-Ruge W, Ulrich J. Morphological adaptive response of the synaptic junctional zones in the human dentate gyrus during aging and alzheimer's disease. *Brain Research*, 517:69, 1990.

[3] Bertoni-Freddari C, Meier-Ruge W, Ulrich J. Quantitative morphology of synaptic plasticity in the aging brain. *Scanning Microsc.*, 2:1027, 1988.

[4] DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in alzheimer's disease: Correlation with cognitive severity. *Ann. Neurology*, 27(5):457, 1990.

[5] Buell SJ, Coleman PD. Dendritic growth in the aged human brain and failure of growth in senile dementia. *Science*, 206:854, 1979.

[6] Flood DG, Coleman PD. Failed compensatory dendritic growth as a pathophysiological process in alzheimer's disease. *Can. J. Neurol. Sci.*, 13:475, 1986.

[7] Katzman R. Alzheimer's disease. *New England Journal of Medicine*, 314(15):964, 1986.

[8] Horn D, Ruppin E, Usher M, Herrmann M. Neural network modeling of memory deterioration in alzheimer's disease. *Preprint*, 1992.

[9] Hansen LA, DeTeresa R, Davies P, Terry RD. Neocortical morphometry, lesion counts, and choline acetyltransferase levels in the age spectrum of alzheimer's disease. *Neurology*, 38:48, 1988.

[10] Drachman DA, O'Donnell BF, Lew RA, Swearer JM. The prognosis in alzheimer's disease. *Arch. Neurol.*, 47:851, 1990.

[11] Zigmond MJ, Abercrombie ED, Berger TW, Grace AA, Stricker EM. Compensations after lesions of central dopaminergic neurons: some clinical and basic implications. *TINS*, 13:290, 1990.

[12] Calne DB, Zigmond MJ. Compensatory mechanisms in degenerative neurologic diseases. *Arch. Neurol.*, 48:361, 1991.

[13] Riederer P, St Wuketich S. Time course of nigrostriatal degeneration in parkinson's disease. *J. Neural Transm.*, 38:277, 1976.

[14] Calne DB, Langston JW. Aetiology of parkinson's disease. *The Lancet*, 1457, 1983.

[15] Mayeux R, Stern Y, Spanton S. Heterogenity in dementia of the alzheimer type: evidence of subgroups. *Neurology*, 35:453, 1985.

[16] Stern Y, Mayeux R, Sano M, Hauser WA, Bush T. Predictors of disease course in patients with probable alzhiemer's disease. *Neurology*, 37:1649, 1987.

[17] Stern Y, Hesdorffer D, Sano M, Mayeux R. Measurement and prediction of functional capacity in alzhemer's disease. *Neurology*, 40:8, 1990.

[18] Perl DP, Pendlebury WW, and Bird ED. Detailed neuropathological evaluation of banked brain specimens submitted with a clinical diagnosis of alzheimer's disease. p 463 in *Third meeting of the international study group on the treatment of memory disorders associated with aging.* (RJ Wurtman, SH Corkin, JH Growdon, ed) Center for brain sciences and metabolism charitable trust, 1984.

[19] Adolfsson R, Gottfries CG, Roos BE, Winblad B. Changes in brain catecholamines in patients with dementia of alzhiemer type. *Br. J. Psychiatry*, 135:216, 1979.

[20] Drevets W, Rubin E. Psychotic symptoms in the longitudinal course of senile dementia of the alzheimer's type. *Biol. Psychiatry*, 25:39, 1989.

[21] Jeste DV, Wragg RE, Salmon DP, Harris MJ, Thal LJ. Cognitive deficits of patients with alzheimer's disease with and without delusions. *Am. J. Psychiatry*, 149:184, 1992.