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Review

Neuroplasticity Failure in Alzheimer's Disease: Bridging the Gap between Plaques and Tangles

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Alzheimer's disease (AD) is a predominantly amnestic dementia that arises on a neuropathological background of amyloid plaques (AP) and neurofibrillary tangles (NFT). A loss of neurons, synapses, and cortical cholinergic innervation constitutes additional features of the disease. Numerous investigations have attempted to isolate the one aspect of the neuropathology that is most closely associated with the cognitive deficits. Such claims have been made for the AP (Cummings et al., 1996), NFT (Arriagada et al., 1992), neuronal loss (Gómez-Isla et al., 1997), synaptic loss (Terry et al., 1991), and cholinergic depletion (Francis et al., 1985). The interactions among these components have been investigated intensively in an attempt to identify a pivotal prime mover for the disease process. Despite numerous attempts, however, a unitary theory that can account for all the clinical and neuropathological features has failed to emerge. This review proposes that a perturbation of neuroplasticity may provide the core of such a unifying theory.

The Memory Loss of AD and Its Continuity with Mild Cognitive Impairment and Aging

AD causes a severe memory loss accompanied by additional but usually less prominent impairments of attention, language, perception, reasoning, and comportment (Price et al., 1993; Morris et al., 1996). A state of dementia becomes identified when these deficits undermine the capacity for independent living. The onset of the dementia in AD is preceded by a transitional "preclinical" period of many years during which relatively isolated memory difficulties exceed those expected on the basis of normal aging, without, however, becoming severe enough to interfere with daily living activities (Linn et al., 1995; Fox et al., 1998). Even "normal" aging does not necessarily imply that memory function has remained intact (Small et al., 1999). In a delayed recall test (Visual Reproduction 2 of the Wechsler Memory Scale–Revised), for example, average performance for 30 year olds corresponds to a score of 31 or better, whereas average performance for 70 year olds corresponds to a score of 15. Thus, normal scores at the age of 70 do not indicate a preservation of memory function. They only indicate that the putative decline has been average for the group of individuals at the same age.

These considerations suggest that four different levels of memory function can be identified during the course of an individual's lifetime. First, a stage of peak performance is reached at some point in the life span. It may be preserved during senescence by rare individuals who are said to enjoy *superior aging*. Second, the majority of individuals experience a decline from this hypothetical peak but are said to show *age-appropriate cognitive functioning* because their performance remains within the range of same-age peers. Third, some individuals complain of forgetfulness and perform significantly worse than their same-age peers without necessarily experiencing a disruption of daily living activities. They are said to be in a state of senescent forgetfulness or *mild cognitive impairment*. (Petersen et al., 1999). Fourth, in still other individuals, the deterioration reaches a level of severity that interferes with daily living activities and that becomes consistent with the diagnostic criteria for *dementia*. Each of these stages is associated with a characteristic pattern of NFT distribution.

The NFT of AD

The NFT are formed by insoluble intracellular polymers of hyperphosphorylated tau, the less phosphorylated forms of which stabilize the microtubules of the axonal cytoskeleton (Trojanowski et al., 1993). The NFT are thought to interfere with cytoskeletal integrity. They induce neuronal dysfunction and, eventually, the destruction of synapses and neurons. Nearly all individuals above the age of 60 have at least a few NFT in the brain (Braak and Braak, 1996). Whenever a brain contains very few NFT, they are always confined to limbic and paralimbic structures such as the hippocampus, the nucleus basalis of Meynert, the amygdala, and the entorhinal–transentorhinal cortex (Figure 1). These parts of the brain play critical roles in the neural control of memory function. This initial *low limbic* stage of NFT distribution may provide a crucial anatomical substrate for the common and relatively selective memory impairments associated with aging. The next level of NFT density can be designated the *high limbic* stage: the NFT become more numerous within limbic areas, they start to form clusters in the immediately adjacent fusiform and inferotemporal gyri, and they appear in additional paralimbic areas such as the temporal pole, insula, orbitofrontal cortex, and the parolfactory gyrus. This stage of NFT distribution may be associated with the states of mild cognitive impairment, senescent forgetfulness and preclinical AD (Delacourte et al., 1999). Only after reaching relatively high densities within limbic, paralimbic, and inferotemporal areas do the NFT eventually emerge and then accumulate in prefrontal and parietotemporal association areas involved in the neural control of language, attention, and perception (Braak and Braak, 1996; Morrison and Hof, 1997; Delacourte et al., 1999). The corresponding *low* and *high neocortical* stages of NFT density are associated with the mild and then severe dementia of AD during which cognitive functions other than memory also become compromised (Arnold et al., 1991; Arriagada et al., 1992; Braak and Braak, 1996; Gómez-Isla et al., 1996; Giannakopoulos et al., 1997; Hyman and Trojanowski, 1997; Morrison and Hof, 1997). The neuropathological criterion for a definitive diagnosis of AD is reached only when NFT clusters emerge in association

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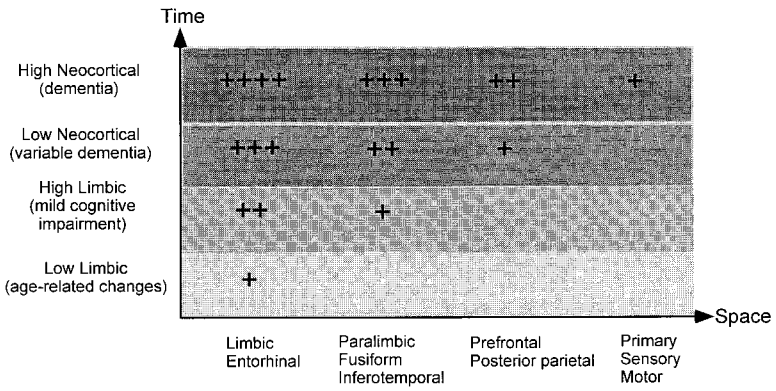

Figure 1. The Progression of NFT in Time and Space and Their Relationship to the Clinical State

One, two, three, and four plus signs refer to low, medium, high, and very high densities of NFT, respectively. The low limbic stage corresponds stages I and II of Braak and Braak (1996), the high limbic stage to their stages III and IV, the low neocortical stage to their stage V, and the high neocortical stage to their stage VI.

neocortex (National Institute on Aging, 1997). In keeping with the relative preservation of sensation and motility in AD, primary sensory–motor areas contain relatively few NFT even in patients with high densities of limbic and neocortical tangles (Figure 1). The generality of this tight correspondence between NFT distribution and mental state has been challenged by reports of rare patients who were not demented despite the presence of NFT at the high neocortical stage (Davis et al., 1999). One possible explanation is that these patients might have experienced a considerable decline of mental function from an exceptionally high baseline without necessarily fulfilling the criteria for dementia. Alternatively, they may have had an unusual neuronal reserve capacity that may have compensated for the impact of the NFT-related neurodegeneration.

The stages of distribution shown in Figure 1 suggest that the vulnerability to NFT formation is highest in the limbic areas of the medial temporal lobe. This vulnerability appears to become transferred along monosynaptic connections from limbic to paralimbic areas, then from paralimbic areas to association neocortex, and only terminally from association neocortex to primary sensory–motor areas. The putative role of axonal connections is highlighted by the fact that subcortical nuclei monosynaptically interconnected with the cerebral cortex (such as the hypothalamus, brainstem raphe, and nucleus locus coeruleus) develop numerous NFT, whereas those with no cortical connections (such as the globus pallidus) do not. The interval between the initial appearance of the NFT in limbic areas and their widespread neocortical distribution in the terminal stages of the dementia may be as long as 50 years (Braak and Braak, 1996).

Amyloid and AD

The AP accumulate in the extracellular space. They contain insoluble fibrils of the amyloid β (Aβ) fragment of a much larger precursor protein (AβPP). The AβPP is a transmembrane protein normally processed by three proteases known as the α, β, and γ secretases. The α secretase splits the AβPP in the middle of the Aβ domain and precludes the release of the plaque-forming Aβ fragment, whereas the β and γ secretases yield moieties that contain the full Aβ fragment. Depending on the site of γ secretase cleavage, the resultant Aβ fragment can be "short" (Aβ1-40) or "long" (Aβ1-42, 43). The long form of Aβ is more insoluble and potentially more neurotoxic (Selkoe, 1994; Yankner, 1996). In at least 95% of patients with AD, onset occurs in late adulthood, usually after the age of 65. In a small minority of cases, the disease has an autosomal dominant pattern of inheritance and can start much earlier. The mutations that cause the dominantly inherited forms of AD are located on chromosomes 21, 14, and 1.

There is no known genetic linkage between AD and tau-processing abnormalities that might lead to NFT formation. In contrast, an impressive body of evidence based on genetics has implicated abnormal amyloid processing in the causation of AD. This evidence can be summarized under six categories. First, mutations in the AβPP gene (chromosome 21) are sufficient to cause early-onset AD. Second, all AD-causing mutations of AβPP, presenilin 1 (PS1 on chromosome 14), and presenilin 2 (PS2 on chromosome 1) lead to the proportionally greater production of the more neurotoxic "long" form of Aβ. Third, trisomy 21 (Down's syndrome), which leads to an overproduction of AβPP and Aβ, invariably leads to the early emergence of AD neuropathology. Fourth, the ϵ4 allele of apolipoprotein E (apoE), a major risk factor for sporadic AD, promotes the precipitation of Aβ into insoluble plaques. Fifth, at least in vitro, Aβ can kill neurons and can induce the phosphorylation of tau. Sixth, the overexpression of AD-causing mutants of AβPP in transgenic mice induces the deposition of amyloid plaques, local damage to neuronal processes, tau phosphorylation, neuronal loss, and perhaps also behavioral deficits (Selkoe, 1994; Olichney et al., 1996; Yankner, 1996; Duff, 1997; Hardy, 1997; Calhoun et al., 1998).

Despite all this supporting evidence, however, an amyloid-based theory of AD pathogenesis faces major challenges: in contrast to NFT, plaques display substantial interindividual variations of distribution, but these variations have no known relationship to the pattern of cognitive deficits; although the initial memory loss indicates the presence of early limbic dysfunction, the initial plaques tend to appear in association neocortex rather than limbic areas; in unusual clinical presentations of AD, the NFT display distribution patterns that fit the expected anatomical substrate of the neuropsychological deficit, whereas the AP do not; extensive neocortical plaque deposits can be seen in nondemented elderly individuals; the correlation between plaque densities and dementia is usually poor; none of

the transgenic animals overexpressing the AD-causing mutations of AβPP has shown NFT formation; and there is no correlation between local densities of plaques and NFT (Arriagada et al., 1992; Guillozet et al., 1995, Soc. Neurosci., abstract; Mackenzie et al., 1996; Giannakopoulos et al., 1997, 1999).

It seems as if the Aβ plaques appear at the wrong time and in the wrong places with respect to the clinical dementia, and there is little evidence that they cause the NFT. One potential resolution to this dilemma may lie in the assumption that amyloid exerts its initial influence in some mobile, circulating form rather than at the sites of plaque deposits (Lambert et al., 1998). However, such an approach would still need to explain how a circulating factor can generate the very specific temporal and spatial pattern of NFT distribution and the specific clinical pattern of the dementia.

Plasticity of the Adult Brain and Its Differential Distribution

The genetics of AD favor a pathogenic mechanism revolving around amyloid deposition, whereas the clinicopathological correlations favor a disease based on NFT. Although numerous mechanisms have been proposed for reconciling these two aspects of AD, none has adequately linked the amyloid deposits to the spatial and temporal patterns of neurofibrillary degeneration. One solution to this dilemma is based on the assumption that these two markers of AD are independent manifestations of a common underlying phenomenon. This review suggests that a prolonged perturbation of neural plasticity may represent such a common denominator. The relationship of plasticity to AD has been discussed in several contexts. It has been suggested that AD is characterized by a loss of plasticity (Buell and Coleman, 1979), that it leads to aberrant plasticity (Scheibel and Tomiyasu, 1978; Masliah et al., 1991), that its pathology is most severe in parts of the brain that have the greatest plasticity (Phelps, 1990; Arendt et al., 1998), and that it may be caused by maladaptive plasticity (Agnati et al., 1992; Neill, 1995). Each of these relationships appears to contribute to the pathogenesis of AD.

Neuroplasticity is a life-long process that mediates the structural and functional reaction of dendrites, axons, and synapses to experience, attrition, and injury. Experience-induced modifications of synaptic strengths, for example, enable the accumulation of a knowledge base that is unique to each individual and provide the critical substrates for adaptation and individuation. The manifestations of neuroplasticity in the adult CNS include alterations of dendritic ramifications, synaptic remodeling, long-term potentiation (LTP), axonal sprouting, neurite extension, synaptogenesis, and neurogenesis. Self-stimulation, learning new associations, and exposure to enriched environments can induce synaptogenesis, synaptic remodeling, and neurogenesis in the adult rodent brain (Black et al., 1989; Kempermann et al., 1998; Klintsova and Greenough, 1999; Rao et al., 1999). Furthermore, electrical kindling by perforant pathway stimulation can induce structural remodeling by increasing the relative number of perforated synapses in the molecular layer of the dentate gyrus (Geinisman et al., 1989).

Plasticity plays a particularly important role in response to injury. Lesions of the entorhino-hippocampal pathway induce intact neurons to sprout collateral branches so that they can occupy the denuded synaptic targets in the molecular layer of the dentate gyrus (Cotman and Nieto-Sampedro, 1984). In the adult monkey, trauma to a forelimb causes a large-scale axonal sprouting and lateral expansion of connections within neocortical somatosensory areas, presumably in response to the loss of the afferent input from the injured limb (Florence et al., 1998). Neuronal death may also induce a compensatory increase of dendritic branching among residual neurons at that site, presumably so that the synaptic inputs that have lost their original targets can be accommodated (Agnati et al., 1992).

The process of reactive synaptogenesis may be of vital importance for replacing terminals that succumb to physiological attrition. The presence of such attrition was demonstrated in the ciliary muscle of the monkey where the half-life of synapse turnover was estimated to be around 18 days (Cotman and Nieto-Sampedro, 1984). There are $\sim$7–8 $\times$ 10^8 synapses in the dentate gyrus of the rat alone (Calhoun et al., 1996). The number of synapses in the human cerebral cortex is undoubtedly many orders of magnitude higher, and these synapses are probably also subject to turnover and structural upkeep. Even if the recycling rate is much slower in the human CNS than in the ciliary muscle of the monkey, the immense number of synapses suggests that synapse turnover and upkeep are likely to constitute major activities of the brain.

Conceptually, these plasticity-related phenomena can be divided into *downstream* processes at the level of axons, synapses, and dendrites and *upstream* regulatory processes at the level of the neuronal perikaryon. The regulation of neuroplasticity is likely to involve signals (such as growth factors) transmitted anterogradely (in the downstream direction) from the perikaryon to dendrites and axonal terminals, and also retrogradely (in the upstream direction) from dendrites, axons, and postsynaptic targets to the perikaryon. Some of these effects are exerted transsynaptically, and many are likely to be mediated by neuroglia (Cotman and Nieto-Sampedro, 1984; Glanzman et al., 1990; Neill, 1995).

Multiple lines of evidence indicate that the potential for neuroplasticity is distributed unevenly in the adult brain so that the propensity for LTP, axonal sprouting, dendritic remodeling, and perhaps reactive synaptogenesis is higher in the limbic system than in other parts of the cerebral cortex (Buell and Coleman, 1979; Neve et al., 1988; Bliss and Collingridge, 1993; Arendt et al., 1995, 1998). Thus, the growth-associated protein GAP-43, which is a marker for axonal sprouting, is most intensely expressed in limbic cortex, especially along the entorhino-hippocampal pathway, suggesting that experience-dependent remodeling and synaptic turnover may be highest in this part of the brain (Neve et al., 1988; Lin et al., 1992). In the adult macaque monkey, the expression levels of mRNAs for brain-derived neurotrophic factor (BDNF) and TrkB are lowest in primary visual cortex, slightly higher in visual association cortex, and highest in the hippocampus and entorhinal cortex (Okuno et al., 1999). Furthermore, plasticity-related increases in the length and branching of the dendritic tree during adulthood appear to be most extensive in

limbic–paralimbic regions such as transentorhinal, entorhinal, and hippocampal cortex of the human brain; somewhat less pronounced in the association neocortex of posterior parietal and prefrontal areas; and undetectable in primary sensory–motor areas (Arendt et al., 1998). This gradient mirrors the temporal and spatial gradient of NFT densities shown in Figure 1, suggesting that elevated levels of plasticity-related cellular activity may increase the vulnerability to neurofibrillary degeneration.

Causes and Risk Factors of AD Influence Plasticity

All genetic backgrounds and risk factors associated with AD can potentially influence neuroplasticity.

Amyloid and Plasticity

Full-length AβPP influences cell–substrate interactions during neurite extension, promotes the formation and maintenance of synapses in the CNS, modulates LTP, and protects neurons against exitotoxic and oxidative insults (Mucke et al., 1994; Storey et al., 1996; Ishida et al., 1997; Small, 1998). The soluble/secreted AβPP product of a secretase processing, known as sAPP, also displays plasticity-promoting properties. This sAPP fragment is released from neurons in response to electrical activity and induces neurite outgrowth, experience-related synaptogenesis, and LTP (Roch et al., 1994; Huber et al., 1997; Ishida et al., 1997; Mattson, 1997).

In contrast to full-length AβPP and sAPP, the Aβ fragment of amyloid, especially its "long" form, is neurotoxic and inhibits axonal sprouting as well as LTP (Roher et al., 1991; Lambert et al., 1998). Trisomy 21 and the AD-causing genetic mutations of AβPP may thus interfere with neural plasticity because they shift the balance of AβPP processing toward the longer and more neurotoxic forms of Aβ (Almkvist et al., 1997; Hardy, 1997). The dendritic atrophy and synaptic rarefaction reported in trisomy 21 may reflect such an impairment of compensatory neuroplasticity (Takashima et al., 1989). Furthermore, transgenic mice overexpressing one of the AD-causing mutations of AβPP show decreased synaptic and dendritic density in the dentate gyrus of the hippocampal formation, a reduced ability for compensatory synaptogenesis in response to injury, impaired LTP, and a corresponding impairment of spatial working memory (Games et al., 1995; Masliah et al., 1995; Chapman et al., 1999).

Presenilins and Plasticity

Presenilin genes are homologous to the *C. elegans sel-12* gene, which facilitates the activity of *lin-12*, a member of the Notch family. Notch is a critical protein involved in neurogenesis and cell fate decisions in the developing nervous system. The *sel-12* mutant phenotype in *C. elegans* can be rescued by normal human PS1 but not by its AD-causing mutants, suggesting that such mutations may interfere with putative Notch-related functions of PS1 (Levitan et al., 1996). Furthermore, the expression of an AD-causing mutant of PS1 causes a depression of nerve growth factor– (NGF-) induced neurite outgrowth in PC12 cells (Furukawa et al., 1998). The AD-causing mutations of PS1 may also interfere with the stabilization and degradation of β-catenin, a protein thought to play a critical role in the formation and maintenance of synaptic junctions, although the exact nature of this relationship appears to vary according to the specific PS1 mutation and the experimental setting (Zhang et al., 1998; Kang et al., 1999). Interestingly, the maturation of TrkB and its BDNF-inducible autophosphorylation become severely impaired in neurons that lack PS1 (Naruse et al., 1998). The AD-causing presenilin mutations could thus perturb plasticity through two mechanisms: an interference with the putative plasticity-related functions of PS1 and a shunting of AβPP processing toward the longer, more neurotoxic Aβ moieties.

ApoE and Plasticity

The ϵ4 allele of apolipoprotein E (apoE) is one of the most intensely investigated risk factors of AD (Roses, 1997). ApoE, encoded by a gene on chromosome 19, promotes axonal growth and synaptogenesis, probably because it regulates the transcellular transport of cholesterol and phospholipids. Following entorhinal cortex lesions, for example, the phase of compensatory synaptogenesis is characterized by a rapid increase of apoE expression by astrocytes within the denervated molecular layer of the dentate gyrus (Poirier, 1994). The importance of apoE for plasticity is supported by experiments which show that apoE-deficient mice display a distinct impairment of reactive synaptogenesis (Masliah et al., 1996; Teter et al., 1999). Individual apoE alleles have differential impacts on plasticity. Thus, the ϵ4 allele, which is a major risk factor for AD, inhibits neurite growth and dendritic plasticity, whereas the ϵ3 allele promotes these processes (Nathan et al., 1994; Arendt et al., 1997).

Estrogen and Plasticity

Estrogen replacement in postmenopausal women decreases the risk of developing AD (Kawas et al., 1997). Estrogens promote axonal and dendritic plasticity in the limbic neurons of male as well as female brains (Ferreira and Caceres, 1991; Lorenzo et al., 1992; Woolley et al., 1996; McEwen et al., 1997; Teter et al., 1999). In female mice, ovariectomy severely impairs the reactive hippocampal synaptogenesis that follows entorhinal damage. This effect is reversed by estrogen replacement (Stone et al., 1998). Postmenopausal estrogen deficiency may thus suppress the potential for neuroplasticity.

Age and Plasticity

The single most important risk factor for AD is age. Age influences both reactive and experience-dependent plasticity. Thus, reactive synaptogenesis in response to complex experience, compensatory synaptogenesis following injury, and the ability to sustain the effects of LTP are all diminished or slowed as a consequence of age (Scheff et al., 1980; Mori, 1993; Lanahan et al., 1997). Indirect evidence based on the examination of the cerebrospinal fluid (CSF) suggests that aging may also shift the complex balance of AβPP metabolism away from the potentially neurotrophic products of α secretase processing and toward the production of neurotoxic moieties containing the intact Aβ fragment (Palmert et al., 1990; van Gool et al., 1994). Age interacts with other variables that influence neuroplasticity. For example, the age-related loss of synaptic and dendritic density becomes substantially more intensified in apoE-deficient mice (Masliah et al., 1996).

Speculations on the Linkage between a High Plasticity Burden and AD Neuropathology

All AD-promoting factors are likely to perturb processes that normally facilitate neuroplasticity. The hypothesis

in this section is based on the assumption that the resultant barriers to neuroplasticity occur at downstream dendritic and synaptic sites and that they trigger a reactive (or compensatory) upstream intensification of plasticity-related perikaryal activity. In other words, AD-promoting factors create a setting where neurons must work harder to meet neuroplasticity needs at their axonal and dendritic terminals. Over many years, such compensatory processes would lead to chronically high and eventually unsustainable levels of plasticity-related cellular activity.

In vivo and in vitro experiments show that high levels of neuroplasticity tend to be associated with the increased expression and phosphorylation of tau (Busciglio et al., 1987; Viereck et al., 1989; Trojanowski et al., 1993; Brion et al., 1994; Black et al., 1996; Lovestone and Reynolds, 1997). For example, the olfactory bulb of the adult rat, a region that continues to show very active neuroplasticity, expresses particularly high levels of the more extensively phosphorylated, fetal forms of tau (Viereck et al., 1989; Lovestone and Reynolds, 1997). Furthermore, transfected PC12 cells overexpressing tau extend neurites more rapidly, and neurite extension in response to NGF is associated with a 10- to 20-fold induction of tau (Drubin et al., 1985; Esmaeli-Azad et al., 1994). In the course of the processes that lead to AD, a chronically high demand for plasticity-related activity could thus upregulate the expression of tau, favor its phosphorylation, and potentially promote the polymerization of tau into NFT. The NFT produced by such a sequence of events would initially appear within limbic–paralimbic neurons, because these neurons have the highest baseline levels of plasticity and would thus have the highest exposure to compensatory upregulations of plasticity-related cellular activity.

The resultant cytoskeletal dysfunction in these limbic–paralimbic neurons would eventually lead to a degeneration of their dendrites and a loss of their synapses at axonal projection targets. The adjacent limbic and paralimbic neurons (many of which share the same connectivity patterns) would then face at least two additional plasticity demands: (1) more reactive synaptogenesis at their projection targets, in order to replace the synapses originally provided by the degenerated axons of adjacent NFT-containing neurons; and (2) more local dendritic remodeling to receive the synapses that can no longer be accommodated by the degenerated dendrites of adjacent NFT-containing neurons. Because of the downstream barriers to plasticity, these attempts at reactive remodeling would be relatively ineffective and would induce an excessive upstream intensification of plasticity-related neuronal activity, eventually leading to the formation of NFT in these additional neurons. This sequence of events would promote the "horizontal" spread of NFT within the tightly interconnected components of limbic–paralimbic cortices and would initiate the relatively slow "limbic" phase of disease progression (from the "Low Limbic" to the "High Limbic" stages in Figure 1).

The loss of dendrites and synapses belonging to limbic–paralimbic neurons would eventually increase the plasticity burden of the association cortices with which they are reciprocally interconnected. These association areas would need to accelerate dendritic remodeling to cope with the loss of inputs from limbic–paralimbic neurons and would also need to remodel axonal endings to cope with the loss of synaptic sites at their limbic targets. This would cause a "vertical" expansion of the disease during which the neurofibrillary degeneration (and eventually cellular death) would spread centrifugally from limbic–paralimbic areas to association neocortex, in keeping with the pattern shown in Figure 1.

In support of this scenario, tangle-bearing hippocampal neurons show more extensive dendritic trees than immediately adjacent tangle-free neurons, suggesting that NFT formation may be accompanied (or preceded) by increased plasticity (Gertz et al., 1990). Furthermore, tau mRNA is increased in the hippocampus (but not in the visual cortex or cerebellum) of patients with AD (Barton et al., 1990). The initial stages of AD are also associated with increased tau in the CSF (Galasko et al., 1997), suggesting that an upregulation of this protein occurs at a time when the NFT are undergoing a steep increase in density and distribution.

Animal experiments show that injury- and denervation-induced neuroplasticity can also lead to an upregulation of AβPP (Banati et al., 1993; Wallace et al., 1993; Beeson et al., 1994; Chauvet et al., 1997). Fimbria–fornix lesions in adult rats, for example, elicit a marked accumulation of AβPP immunoreactivity in the denervated areas within the hippocampus (Beeson et al., 1994). Such reactive AβPP accumulation may be quite selective. In the case of the fimbria–fornix lesions, it seems to occur predominantly in the CA1 region but not in the dentate gyrus (Beeson et al., 1994). In the course of events leading to AD, an initial upregulation of AβPP would be expected to occur at sites of maximal plasticity burden, namely in limbic–paralimbic areas and their axonal projection targets. This AβPP would then be processed into the sAPP and Aβ moieties, giving rise to complex combinations of neurotrophic and neurotoxic effects. The released Aβ would first have a soluble form and would diffuse within the extracellular fluid in the form of 10–100 kDa monomers and oligomers (Kuo et al., 1996). Upon exceeding local concentration thresholds, this Aβ would be expected to form fibrils and condense into initially inert diffuse plaques that would eventually mature into neurotoxic structures. The formation of plaques by local condensation after the diffusion of the amyloid from sites of upregulation, the fact that these sites can overlap with NFT-prone limbic–paralimbic neurons or their widespread projection targets, the apparent regional selectivity of plasticity-induced AβPP accumulation, and the initial inertness of the deposited amyloid may explain why plaques do not mirror the distribution of the NFT, and why they do not necessarily display a spatial and temporal distribution that fits the clinical features of the dementia.

The premature development of NFT and Aβ deposits in the brains of ex-boxers provides further circumstantial support for the contention that a heightened state of neuroplasticity (in this case, injury-induced) can trigger the neuropathological changes of AD (Tokuda et al., 1991; Geddes et al., 1996). This is perhaps why head injury and stroke have both been implicated as risk factors for AD (Salib and Hillier, 1997; Snowdon et al., 1997). However, such relationships are probably relevant only when the injury is widespread and chronic, and when it

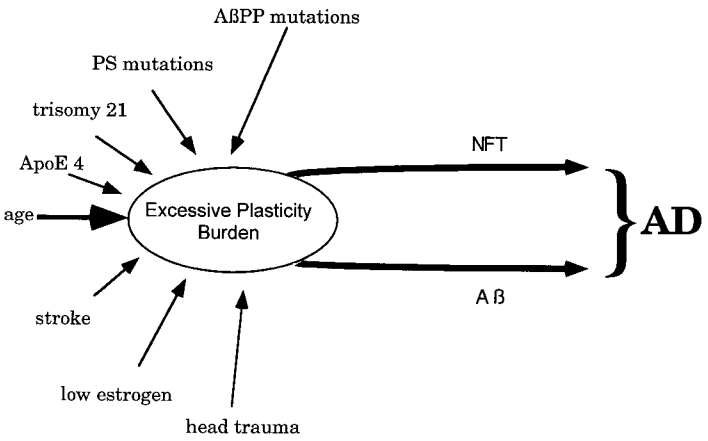

Figure 2. Multiple Factors Increase the Neuroplasticity Burden

Eventually, the excessive neuroplasticity burden triggers plaque and NFT formation. AD is said to exist when the density of both of these histopathological markers exceeds a certain threshold and when they are accompanied by dementia. Abbreviations: Aβ, β amyloid; AβPP, β amyloid precursor protein; ApoE, apolipoprotein E; NFT, neurofibrillary tangle; PS, presenilin.

occurs on a background of additional factors that erect downstream barriers to neuroplasticity. Otherwise, all neuronal diseases would eventually lead to AD pathology.

A severe depletion of cortical cholinergic innervation is one of the most consistent features in the neuropathology of AD (Geula and Mesulam, 1999). The cholinergic innervation of the cerebral cortex arises from the nucleus basalis of Meynert, a limbic structure that maintains an unusually high level of plasticity into late adulthood (Arendt et al., 1995). Neurons of the nucleus basalis are consequently among the very first cells of the brain to display an accumulation initially of hyperphosphorylated tau and then of NFT (Mesulam, 1996). Numerous experiments have shown that cholinergic neurotransmission plays an essential role in supporting reactive and experience-induced synaptic reorganization in the cerebral cortex (Baskerville et al., 1997; Kilgard and Merzenich, 1998; Zhu and Waite, 1998). Furthermore, cortical cholinergic innervation also promotes the α secretase pathway and therefore the release of the neurotrophic sAPP moieties (Nitsch et al., 1992). The early loss of cholinergic innervation in AD could thus contribute to the acceleration of the pathological process by further jeopardizing the potential for neuroplasticity in the cerebral cortex, both directly and through changes in AβPP metabolism.

Conclusions

"Neuroplasticity" is a generic term referring to processes of vital importance for the structural upkeep of the brain and for the functional adaptation of the organism to the environment. The evidence reviewed above leads to the hypothesis that the remote initiators of AD may be traced to factors that erect physiological barriers to the downstream manifestations of neuroplasticity, and that the NFT and AP represent independent byproducts of initially compensatory but eventually excessive and maladaptive plasticity-related cellular activity. The exceedingly complex events associated with neuroplasticity are influenced by multiple genetic and environmental factors. Consequently, a large number of variables can determine the ease (or difficulty) with which the neuroplasticity demands are met and also the time at which perturbations of neuroplasticity reach the critical threshold and duration needed to trigger the events that lead to AD.

The biological capacity for plasticity decreases with age, explaining why age is the single most important and universal risk factor for AD. According to this formulation, the AD of old age may not be a disease at all but the inevitable manifestation of a failure to keep up with the increasingly more burdensome work of plasticity. Other factors such as trisomy 21, the ϵ4 allele of apoE, estrogen deficiency, head trauma, and the AD-related mutations of AβPP, PS1, and PS2 accelerate the time course of the events leading to AD by increasing the burden of neuroplasticity (Figure 2). The fact that all of these factors operate through a common downstream mechanism helps to explain how the numerous genotypes of AD cause an identical clinical and neuropathological disease phenotype. Genetic mutations do not really cause AD; they simply accelerate the temporal course of events that lead to plasticity failure and therefore lower the age at which the pathological process begins to gather momentum. The advanced cognitive and mnemonic activities of the human brain impose a very high plasticity burden. The combination of this property with a long life span may endow the human brain with its unique susceptibility to AD.

The first wave of AD therapy has aimed to reverse the depletion of cortical cholinergic neurotransmission. Subsequent strategies may aim to inhibit tau polymerization and Aβ formation. For reasons that have been described above, such interventions may not be entirely successful unless the underlying plasticity failure is also addressed. The proposed role of plasticity suggests that important insights related to the pathophysiology and prevention of AD may come from the fields of developmental biology. One of the most important goals will be to understand the processes that influence plasticity in the adult human brain and to determine whether their vulnerability to aging and to the other AD-causing factors can be modified.

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References

Agnati, L.F., Zoli, M., Biagini, G., and Fuxe, K. (1992). Neuronal plasticity and ageing processes in the frame of the 'Red Queen Theory'. Acta Physiol. Scand. *145*, 301–309.

Almkvist, O., Basun, H., Wagner, S.L., Rowe, B.A., Wahlund, L.-O., and Lannfelt, L. (1997). Cerebrospinal fluid levels of α-secretase-cleaved soluble amyloid precursor protein mirror cognition in a Swedish family with Alzheimer disease and a gene mutation. Arch. Neurol. *54*, 641–644.

Arendt, T., Brückner, M.K., Bigl, V., and Marcova, L. (1995). Dendritic reorganization in the basal forebrain under degenerative conditions and its defects in Alzheimer's disease. III. The basal forebrain compared with other subcortical areas. J. Comp. Neurol. *351*, 223–246.

Arendt, T., Schindler, C., Brückner, M.K., Eschrich, K., Bigl, V., Zedlick, D., and Marcova, L. (1997). Plastic neuronal remodeling is impaired in patients with Alzheimer's disease carrying apolipoprotein ϵ4 allele. J. Neurosci. *17*, 516–529.

Arendt, T., Brückner, M.K., Gertz, H.-J., and Marcova, L. (1998). Cortical distribution of neurofibrillary tangles in Alzheimer's disease matches the pattern of neurons that retain their capacity of plastic remodeling in the adult brain. Neuroscience *83*, 991–1002.

Arnold, S.E., Hyman, B.T., Flory, J., Damasio, A.R., and van Hoesen, G.W. (1991). The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb. Cortex *1*, 103–116.

Arriagada, P.V., Growdon, J.H., Hedley-Whyte, E.T., and Hyman, B.T. (1992). Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology *42*, 631–639.

Banati, R.B., Gehrmann, J., Czech, C., Monning, U., Jones, L.L., Konig, G., Beyreuther, K., and Kreutzberg, G.W. (1993). Early and de novo synthesis of Alzheimer beta A4-amyloid precursor protein (APP) in activated microglia. Glia *9*, 199–210.

Barton, A.J., Harrison, P.J., Najlerahim, A., Haffernan, J., McDonald, B., Robinson, J.R., Davies, D.C., Harrison, W.J., Mitra, P., and Hardy, J.A. (1990). Increased tau messenger RNA in Alzheimer's disease hippocampus. Am. J. Pathol. *137*, 497–502.

Baskerville, K.A., Schweitzer, J.B., and Herron, P. (1997). Effects of cholinergic depletion on experience-dependent plasticity in the cortex of the rat. Neuroscience *80*, 1159–1169.

Beeson, J.G., Shelton, E.R., Chan, H.W., and Gage, F.H. (1994). Age and damage induced changes in amyloid protein precursor immunohistochemistry in the rat brain. J. Comp. Neurol. *342*, 69–77.

Black, M.M., Slaughter, T., Moshiach, S., Obrocka, M., and Fischer, I. (1996). Tau is enriched on dynamic microtubules in the distal region of growing axons. J. Neurosci. *16*, 3601–3619.

Black, J.E., Polinsky, M., and Greenough, W.T. (1989). Progressive failure of cerebral angiogenesis supporting neural plasticity in aging rats. Neurobiol. Aging *10*, 353–358.

Bliss, T.V., and Collingridge, G.L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. Nature *361*, 31–39.

Braak, H., and Braak, E. (1996). Evolution of the neuropathology of Alzheimer's disease. Acta Neurol. Scand. *165 (suppl.)*, 3–12.

Brion, J.-P., Octave, J.N., and Couck, A.M. (1994). Distribution of the phosphorylated microtubule-associated protein tau in developing cortical neurons. Neuroscience *63*, 895–909.

Buell, S.J., and Coleman, P.D. (1979). Dendritic growth in the aged human brain and failure of growth in senile dementia. Science *206*, 854–856.

Busciglio, J., Ferreira, A., Steward, O., and Caceres, A. (1987). An immunocytochemical and biochemical study of the microtubule-associated protein tau during post-lesion afferent reorganization in the hippocampus of adult rats. Brain Res. *419*, 244–252.

Calhoun, M.E., Jucker, M., Martin, L.J., Thinakaran, G., Price, D.L., and Mouton, P.R. (1996). Comparative evaluation of synaptophysin-based methods for quantitation of synapses. J. Neurocytol. *25*, 821–828.

Calhoun, M.E., Wiederhold, K.H., Abramowski, D., Phinney, A.L., Probst, A., Sturchler-Pierrat, C., Staufenbiel, M., Sommer, B., and Jucker, M. (1998). Neuron loss in APP transgenic mice. Nature *395*, 755–756.

Chapman, P.F., White, G.L., Jones, M.J., Cooper-Blacketer, D., Marshall, V.J., Irizarry, M., Younkin, L., Good, M.A., Bliss, T.V.P., Hyman, B.T., et al. (1999). Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. Nat. Neurosci. *2*, 271–276.

Chauvet, N., Apert, C., Dumoulin, A., Epelbaum, J., and Alonso, G. (1997). Mab22C11 antibody to amyloid precursor protein recognizes a protein associated with specific astroglial cells of the rat central nervous system characterized by their capacity to support axonal outgrowth. J. Comp. Neurol. *377*, 550–564.

Cotman, C.W., and Nieto-Sampedro, M. (1984). Cell biology of synaptic plasticity. Science *225*, 1287–1294.

Cummings, B.J., Pike, C.J., Shankle, R., and Cotman, C.W. (1996). β-amyloid deposition and other measures of neuropathology predict cognitive status in Alzheimer's disease. Neurobiol. Aging *17*, 921–933.

Davis, D.G., Schmitt, A., Wekstein, D.R., and Merkesberry, W.R. (1999). Alzheimer neuropathologic alterations in aged cognitively normal subjects. J. Neuropathol. Exp. Neurol. *58*, 376–388.

Delacourte, A., David, J.P., Sergeant, N., Buée, L., Wattez, A., Vermersch, P., Ghozali, F., Fallet-Bianco, C., Pasquier, F., Lebert, F., et al. (1999). The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology *52*, 1158–1165.

Drubin, D.G., Feinstein, S.C., Shooter, E.M., and Kirschner, M.W. (1985). Nerve growth factor–induced neurite outgrowth in PC12 cells involves the coordinate induction of microtubule assembly and assembly-promoting factors. J. Cell Biol. *101*, 1799–1807.

Duff, K. (1997). Alzheimer transgenic mouse models come of age. Trends Neurosci. *20*, 279–280.

Esmaeli-Azad, B., McCarty, J.H., and Feinstein, S.C. (1994). Sense and antisense transfection analysis of tau function: tau influences net microtubule assembly, neurite outgrowth and neuritic stability. J. Cell Sci. *107*, 869–879.

Ferreira, A., and Caceres, A. (1991). Estrogen-enhanced neurite growth: evidence for a selective induction of Tau and stable microtubules. J. Neurosci. *11*, 392–400.

Florence, S.L., Taub, H.B., and Kaas, J.H. (1998). Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. Science *282*, 1117–1121.

Fox, N.C., Warrington, E.K., Seiffer, A.L., Agnew, S.K., and Rossor, M.N. (1998). Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease: a longitudinal prospective study. Brain *121*, 1631–1639.

Francis, P.T., Palmer, A.M., Sims, N.R., Bowen, D.M., Davison, A.N., Esiri, M.M., Neary, D., Snowden, J.S., and Wilcock, G.K. (1985). Neurochemical studies of early-onset Alzheimer's disease. Possible influence on treatment. N. Engl. J. Med. *313*, 7–11.

Furukawa, K., Guo, Q., Schellenberg, G.D., and Mattson, M.P. (1998). Presenilin-1 mutation alters NGF-induced neurite outgrowth, calcium homeostasis, and transcription factor (AP-1) activation in PC12 cells. J. Neurosci. Res. *52*, 618–624.

Galasko, D., Clark, C., Chang, L., Miller, B., Green, R.C., Motter, R., and Seubert, P. (1997). Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease. Neurology *48*, 632–635.

Games, D., Adams, D., Alessandrini, R., Barbour, R., Berthelette, P., Blackwell, C., Carr, T., Clemens, J., Donaldson, T., Gillespie, F., et al. (1995). Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein. Nature *373*, 523–527.

Geddes, J.F., Vowles, G.H., Robinson, S.F., and Sutcliffe, J.C. (1996). Neurofibrillary tangles, but not Alzheimer-type pathology, in a young boxer. Neuropathol. Appl. Neurobiol. *22*, 12–16.

Geinisman, Y., Morrell, F., and de Toledo-Morrell, L. (1989). Perforated synapses on double-headed dendritic spines: a possible structural substrate of synaptic plasticity. Brain Res. *480*, 326–329.

Gertz, H.-J., Krüger, H., Patt, S., and Cervos-Navarro, J. (1990). Tangle-bearing neurons show more extensive dendritic trees than

tangle-free neurons in area CA1 of the hippocampus in Alzheimer's disease. Brain Res. *548*, 260–266.

Geula, C., and Mesulam, M.-M. (1999). Cholinergic systems in Alzheimer's disease. In Alzheimer Disease, R.D. Terry et al., eds. (Philadelphia: Lippincott Williams & Wilkins), pp. 269–292.

Giannakopoulos, P., Hof, P.R., Michel, J.P., Guimon, J., and Bouras, C. (1997). Cerebral cortex pathology in aging and Alzheimer's disease: a quantitative survey of large hospital-based geriatric and psychiatric cohorts. Brain Res. Rev. *25*, 217–245.

Giannakopoulos, P., Gold, G., Duc, M., Michel, J.-P., Hof, P.R., and Bouras, C. (1999). Neuroanatomical correlates of visual agnosia in Alzheimer's disease. A clinicopathologic study. Neurology *52*, 71–77.

Glanzman, D.L., Kandel, E.R., and Schacher, S. (1990). Target-dependent structural changes accompanying long-term synaptic facilitation in Aplysia neurons. Science *249*, 799–802.

Gómez-Isla, T., Price, J.L., McKeel, D.W., Jr., and Morris, J.C. (1996). Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. J. Neurosci. *16*, 4491–4500.

Gómez-Isla, T., Hollister, R., West, H., Mui, S., Growdon, J.H., Petersen, R.C., Parisi, J.E., and Hyman, B.T. (1997). Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. Ann. Neurol. *41*, 17–24.

Hardy, J. (1997). Amyloid, the presenilins and Alzheimer's disease. Trends Neurosci. *20*, 154–159.

Huber, G., Bailly, Y., Martin, J.R., Mariani, J., and Brugg, B. (1997). Synaptic β-amyloid precursor proteins increase with learning capacity in rats. Neuroscience *80*, 313–320.

Hyman, B.T., and Trojanowski, J.Q. (1997). Editorial on consensus recommendations for the postmortem diagnosis of Alzheimer's disease from the National Institute on Aging and the Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. J. Neuropathol. Exp. Neurol. *56*, 1095–1097.

Ishida, A., Furukawa, K., Keller, J.N., and Mattson, M.P. (1997). Secreted form of β-amyloid precursor protein shifts the frequency dependency for induction of LTD, and enhances LTP in hippocampal slices. Neuroreport *8*, 2133–2137.

Kang, D.E., Soriano, S., Frosch, M.P., Collins, T., Naruse, S., Sisodia, S.S., Leibowitz, G., Levine, F., and Koo, E.H. (1999). Presenilin 1 facilitates the constitutive turnover of beta-catenin: differential activity of Alzheimer's disease–linked PS1 mutants in the beta-catenin-signaling pathway. J. Neurosci. *19*, 4229–4237.

Kawas, C., Resnick, S., Morrison, A., Brookmeyer, R., Corrada, M., Zonderman, A., Bacal, C., Lingle, D.D., and Metter, E. (1997). A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore longitudinal study of aging. Neurol. *48*, 1517–1521.

Kempermann, G., Brandon, E.P., and Gage, F.H. (1998). Environmental stimulation of 129/SvJ mice causes increased cell proliferation and neurogenesis in the adult dentate gyrus. Curr. Biol. *8*, 939–942.

Kilgard, M.P., and Merzenich, M.M. (1998). Cortical map reorganization enabled by nucleus basalis activity. Science *279*, 1714–1718.

Klintsova, A.Y., and Greenough, W.T. (1999). Synaptic plasticity in cortical systems. Curr. Opin. Neurobiol. *9*, 203–208.

Kuo, Y.M., Emmerling, M.R., Vigo-Pelfrey, C., Kasunic, T.C., Kirkpatrick, J.B., Murdoch, G.H., Ball, M.J., and Roher, A.E. (1996). Water-soluble Aβ (N-40, N-42) oligomers in normal and Alzheimer disease brains. J. Biol. Chem. *271*, 4077–4081.

Lambert, M.P., Barlow, A.K., Chromy, B., Edwards, C., Freed, R., Liosatos, M., Morgan, T.E., Rozovsky, I., Trommer, B., Viola, K.A., et al. (1998). Diffusable, nonfibrillar ligands derived from Aβ 1–42 are potent central nervous system neurotoxins. Proc. Natl. Acad. Sci. USA *95*, 6448–6453.

Lanahan, A., Lyford, G., Stevenson, G.S., Worley, P.F., and Barnes, C.A. (1997). Selective alteration of long-term potentiation–induced transcriptional response in hippocampus of aged, memory-impaired rats. J. Neurosci. *17*, 2876–2885.

Levitan, D., Doyle, T.G., Brousseau, D., Lee, M.K., Thinakaran, G., Slunt, H.H., Sisodia, S.S., and Greenwald, I. (1996). Assessment of normal and mutant human presenilin function in Caenorhabditis. roc. Proc. Natl. Acad. Sci. USA *93*, 14940–14944.

Lin, L.-H., Bock, S., Carpenter, K., Rose, M., and Norden, J.J. (1992). Synthesis and transport of GAP-43 in entorhinal cortex of neurons and perforant pathway during lesion-induced sprouting and reactive synaptogenesis. Mol. Brain Res. *14*, 147–153.

Linn, R.T., Wolf, P.A., Bachman, D.L., Knoefel, J.E., Cobb, J.L., Belanger, A.J., Kaplan, E.F., and D'Agostino, R.B. (1995). The 'preclinical phase' of probable Alzheimer's disease. A 13-year prospective study of the Framingham cohort. Arch. Neurol. *52*, 485–490.

Lorenzo, A., Diaz, H., Carrer, H., and Caceres, A. (1992). Amygdala neurons in vitro: neurite growth and effects of estradiol. J. Neurosci. Res. *33*, 418–435.

Lovestone, S., and Reynolds, C.H. (1997). The phosphorylation of tau: a critical stage in neurodevelopment and neurodegenerative processes. Neuroscience *78*, 309–324.

Mackenzie, I.R.A., McLachlan, R.S., Kubu, C.S., and Miller, L.A. (1996). Prospective neuropsychological assessment of nondemented patients with biopsy proven senile plaques. Neurology *46*, 425–429.

Masliah, E., Mallory, M., Hansen, L., Alford, M., Albright, T., DeTeresa, R., Terry, R., Baudier, J., and Saitoh, T. (1991). Patterns of aberrant sprouting in Alzheimer's disease. Neuron *6*, 729–739.

Masliah, E., Mallory, M., Alford, M., Ge, N., and Mucke, L. (1995). Abnormal synaptic regeneration in hAPP695 transgenic and APOE knockout mice. In Research Advances in Alzheimer's Disease and Related Disorders, K. Iqbal, J.A. Mortimer, B. Winblad, and H.M. Wisniewski, eds. (New York: John Wiley and Sons), pp. 405–414.

Masliah, E., Mallory, M., Alford, M., Veinbergs, I., and Roses, A.D. (1996). Apolipoprotein E role in maintaining the integrity of the aging central nervous system. In Apolipoprotein E and Alzheimer's Disease, A.D. Roses, K.H. Weisgraber, and Y. Christen, eds. (Berlin: Springer-Verlag), pp. 59–73.

Mattson, M.P. (1997). Cellular actions of beta-amyloid precursor protein and its soluble and fibrillogenic derivatives. Physiol. Rev. *77*, 1081–1132.

McEwen, B.S., Alves, S.E., Bulloch, K., and Weilan, N.G. (1997). Ovarian steroids and the brain: implications for cognition and aging. Neurology *48 (suppl.)*, S8–S15.

Mesulam, M.-M. (1996). The systems-level organization of cholinergic innervation in the cerebral cortex and its alterations in Alzheimer's disease. Prog. Brain Res. *109*, 285–298.

Mori, N. (1993). Toward understanding of the molecular basis of loss of neuronal plasticity in ageing. Age Ageing *22*, S5–S18.

Morris, J.C., Storandt, M., McKeel, D.W., Jr., Rubin, E.H., Price, J.L., Grant, E.A., and Berg, L. (1996). Cerebral amyloid deposition and diffuse plaques in "normal" aging: evidence for presymptomatic and very mild Alzheimer's disease. Neurology *46*, 707–719.

Morrison, J.H., and Hof, P.R. (1997). Life and death of neurons in the aging brain. Science *278*, 412–419.

Mucke, L., Masliah, E., Johnson, W.B., Ruppe, M.D., Alford, M., Rockenstein, E.M., Forss-Petter, S., Pietropaolo, M., Mallory, M., and Abraham, C.R. (1994). Synaptotrophic effects of human amyloid β protein precursors in the cortex of transgenic mice. Brain Res. *666*, 151–167.

Naruse, S., Thinakaran, G., Luo, J.J., Kusiak, J.W., Tomita, T., Iwatsubo, T., Qian, X., Ginty, D.D., Price, D.L., Borchelt, D.R., et al. (1998). Effects of PS1 deficiency on membrane protein trafficking in neurons. Neuron *21*, 1213–1221.

Nathan, B.P., Bellosta, S., Sanan, D.A., Weisgraber, K.H., Mahley, R.W., and Pitas, R.E. (1994). Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. Science *264*, 850–852.

The National Institute on Aging and the Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. (1997). Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. Neurobiol. Aging *18*, S1–S2.

Neill, D. (1995). Alzheimer's disease: maladaptive synaptoplasticity hypothesis. Neurodegeneration *4*, 217–232.

Neve, R.L., Finch, E.A., Bird, E.D., and Benowitz, L.I. (1988). Growth-associated protein GAP-43 is expressed selectively in associative

regions of the adult human brain. Proc. Natl. Acad. Sci. USA *85*, 3638–3642.

Nitsch, R.M., Slack, B.E., Wurtman, R.J., and Growdon, J.H. (1992). Release of Alzheimer amyloid precursor derivatives stimulated by activation of muscarinic acetylcholine receptors. Science *258*, 304–307.

Okuno, H., Tokuyama, W., Li, Y.X., Hashimoto, T., and Miyashita, Y. (1999). Quantitative evaluation of neurotrophin and trk mRNA expression in visual and limbic areas along the occipito-temporo-hippocampal pathway in adult macaque monkeys. J. Comp. Neurol. *408*, 378–398.

Olichney, J.M., Hansen, L.A., Galasko, D., Saitoh, T., Hofstetter, C.R., Katzman, R., and Thal, L.J. (1996). The apolipoprotein E ϵ4 allele is associated with increased neuritic plaques and cerebral amyloid angiopathy in Alzheimer's disease and Lewy body variant. Neurology *47*, 190–196.

Palmert, M.R., Usiak, M., Mayeux, R., Raskind, M., Tourtelotte, W.W., and Younkin, S.G. (1990). Soluble derivatives of the beta amyloid protein precursor in cerebrospinal fluid: alterations in normal aging and in Alzheimer's disease. Neurology *40*, 1028–1034.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., and Kokmen, E. (1999). Mild cognitive impairment. Clinical characterization and outcome. Arch. Neurol. *56*, 303–308.

Phelps, C.H. (1990). Neural plasticity in aging and Alzheimer's disease: some selected comments. Prog. Brain Res. *86*, 3–9.

Poirier, J. (1994). Apolipoprotein E in animal models of CNS injury and in Alzheimer's disease. Trends Neurosci. *17*, 525–530.

Price, B.H., Gurvit, H., Weintraub, S., Geula, C., Leimkuhler, E., and Mesulam, M. (1993). Neuropsychological patterns and language deficits in 20 consecutive cases of autopsy-confirmed Alzheimer's disease. Arch. Neurol. *50*, 931–937.

Rao, B.S.S., Raju, T.R., and Meti, B.L. (1999). Increased numerical density of synapses in CA3 region of hippocampus and molecular layer of motor cortex after self-stimulation rewarding experience. Neuroscience *91*, 799–803.

Roch, J.-M., Masliah, E., Roch-Levecq, A.-C., Sundsmo, M.P., Otero, D.A.C., Veinbergs, I., and Saitoh, T. (1994). Increase of synaptic density and memory retention by a peptide representing the trophic domain of the amyloid β/A4 protein precursor. Proc. Natl. Acad. Sci. USA *91*, 7450–7454.

Roher, A.E., Ball, M.J., Bhave, S.V., and Wakade, A.R. (1991). β-amyloid from Alzheimer disease brains inhibit sprouting and survival of sympathetic neurons. Biochem. Biophys. Res. Commun. *174*, 572–579.

Roses, A.D. (1997). The predictive value of APOE genotyping in the early diagnosis of dementia of the Alzheimer type: data from three independent series. In Alzheimer's Disease: Biology, Diagnosis and Therapeutics, K. Iqbal, B. Winblad, T. Nishimura, M. Takeda, and H.M. Wisniewski, eds. (New York: John Wiley and Sons), pp. 85–91.

Salib, E., and Hillier, V. (1997). Head injury and the risk of Alzheimer's disease: a case control study. Int. J. Geriatr. Psychiatry *12*, 363–368.

Scheff, S.W., Bernardo, L.S., and Cotman, C.W. (1980). Decline in reactive fiber growth in the dentate gyrus of aged rats as compared to young adult rats following entorhinal cortex removal. Brain Res. *199*, 21–38.

Scheibel, A.B., and Tomiyasu, U. (1978). Dendritic sprouting in Alzheimer's presenile dementia. Exp. Neurol. *60*, 1–8.

Selkoe, D.J. (1994). Alzheimer's disease: a central role for amyloid. J. Neuropathol. Exp. Neurol. *53*, 438–447.

Small, D.H. (1998). The role of the amyloid precursor (APP) in Alzheimer's disease: does the normal function of APP explain the topography of neurodegeneration? Neurochem. Res. *23*, 795–806.

Small, S.A., Stern, Y., Tang, M., and Mayeux, R. (1999). Selective decline in memory function among healthy elderly. Neurology *52*, 1392–1396.

Snowdon, D.A., Greiner, L.H., Mortimer, J.A., Riley, K.P., Greiner, P.A., and Markesbery, W.R. (1997). Brain infarction and the clinical expression of Alzheimer's disease. The nun study. JAMA *277*, 813–817.

Stone, D.J., Rozovsky, I., Morgan, T.E., Anderson, C.P., and Finch, C.E. (1998). Increased synaptic sprouting in response to estrogen via an apolipoprotein E–dependent mechanism: implications for Alzheimer's disease. J. Neurosci. *18*, 3180–3185.

Storey, E., Beyreuther, K., and Masters, C.L. (1996). Alzheimer's disease amyloid precursor protein on the surface of cortical neurons in primary culture co-localizes with adhesion patch components. Brain Res. *735*, 217–231.

Takashima, S., Ieshima, A., Nakamura, H., and Becker, L.E. (1989). Dendrites, dementia and the Down syndrome. Brain Dev. *11*, 131–133.

Terry, R.D., Masliah, E., Salmon, D.P., Butters, N., DeTeresa, R., Hill, R., Hansen, L.A., and Katzman, R. (1991). Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann. Neurol. *30*, 572–580.

Teter, B., Harris-White, M.E., Frautschy, S.A., and Cole, G.M. (1999). Role of apolipoprotein E and estrogen in mossy fiber sprouting in hippocampal slice cultures. Neuroscience *91*, 1009–1016.

Tokuda, T., Ikeda, S., Yanagisawa, N., Ihara, Y., and Glenner, G.G. (1991). Re-examination of ex-boxer's brains using immunohistochemistry with antibodies to amyloid beta-protein and tau protein. Acta Neuropathol. *82*, 280–285.

Trojanowski, J.Q., Schmidt, M.L., Shin, R.-W., Bramblett, G.T., Goedert, M., and Lee, V.M.-Y. (1993). From pathological marker to potential mediator of neuronal dysfunction and degeneration in Alzheimer's disease. Clin. Neurosci. *1*, 184–191.

van Gool, W.A., Schenk, D.B., and Bolhuis, P.A. (1994). Concentrations of beta-amyloid protein in cerebrospinal fluid increase with age in patients free from neurodegenerative disease. Neurosci. Lett. *172*, 122–124.

Viereck, C., Tucker, R.P., and Matus, A. (1989). The adult rat olfactory system expresses microtubule-associated proteins found in the developing brain. J. Neurosci. *9*, 3547–3557.

Wallace, W., Ahlers, S.T., Gotlib, J., Bragin, V., Sugar, J., Gluck, R., Shea, P.A., Davis, K.L., and Haroutunian, V. (1993). Amyloid precursor protein in the cerebral cortex is rapidly and persistently induced by loss of subcortical innervation. Proc. Natl. Acad. Sci. USA *90*, 8712–8716.

Woolley, C.S., Wenzel, H.J., and Schwartzkroin, P.A. (1996). Estradiol increases the frequency of multiple synapse boutons in the hippocampal CA1 region of the adult female rat. J. Comp. Neurol. *373*, 108–117.

Yankner, B.A. (1996). Mechanisms of neuronal degeneration in Alzheimer's disease. Neuron *16*, 921–932.

Zhang, Z., Hartmann, H., Do, V.M., Abramowski, D., Struchler-Pierrat, C., Staufenbiel, M., Sommer, B., van de Wetering, M., Clevers, H., Saftig, P., et al. (1998). Destabilization of beta-catenin by mutations in presenilin-1 potentiates neuronal apoptosis. Nature *395*, 698–702.

Zhu, X.O., and Waite, P.M.E. (1998). Cholinergic depletion reduces plasticity of barrel field cortex. Cereb. Cortex *8*, 63–72.