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COMMENTARY

ALZHEIMER'S DISEASE AS A DISORDER OF MECHANISMS UNDERLYING STRUCTURAL BRAIN SELF-ORGANIZATION

T. ARENDT*

Paul Flechsig Institute of Brain Research, Department of Neuroanatomy, University of Leipzig, Jahnallee 59, D-04109 Leipzig, Germany

Abstract—Mental function has as its cerebral basis a specific dynamic structure. In particular, cortical and limbic areas involved in "higher brain functions" such as learning, memory, perception, self-awareness and consciousness continously need to be self-adjusted even after development is completed. By this lifelong self-optimization process, the cognitive, behavioural and emotional reactivity of an individual is stepwise remodelled to meet the environmental demands. While the presence of rigid synaptic connections ensures the stability of the principal characteristics of function, the variable configuration of the flexible synaptic connections determines the unique, non-repeatable character of an experienced mental act. With the increasing need during evolution to organize brain structures of increasing complexity, this process of selective dynamic stabilization and destabilization of synaptic connections becomes more and more important. These mechanisms of structural stabilization and labilization underlying a lifelong synaptic remodelling according to experience, are accompanied, however, by increasing inherent possibilities of failure and may, thus, not only allow for the evolutionary aquisition of "higher brain function" but at the same time provide the basis for a variety of neuropsychiatric disorders.

It is the objective of the present paper to outline the hypothesis that it might be the disturbance of structural brain self-organization which, based on both genetic and epigenetic information, constantly "creates" and "re-creates" the brain throughout life, that is the defect that underlies Alzheimer's disease (AD). This hypothesis is, in particular, based on the following lines of evidence. (1) AD is a synaptic disorder. (2) AD is associated with aberrant sprouting at both the presynaptic (axonal) and postsynaptic (dendritic) site. (3) The spatial and temporal distribution of AD pathology follows the pattern of structural neuroplasticity in adulthood, which is a developmental pattern. (4) AD pathology preferentially involves molecules critical for the regulation of modifications of synaptic connections, i.e. "morphoregulatory" molecules that are developmentally controlled, such as growth-inducing and growth-associated molecules, synaptic molecules, adhesion molecules, molecules involved in membrane turnover, cytoskeletal proteins, etc. (5) Life events that place an additional burden on the plastic capacity of the brain or that require a particularly high plastic capacity of the brain might trigger the onset of the disease or might stimulate a more rapid progression of the disease. In other words, they might increase the risk for AD in the sense that they determine when, not whether, one gets AD. (6) AD is associated with a reactivation of developmental programmes that are incompatible with a differentiated cellular background and, therefore, lead to neuronal death. From this hypothesis, it can be predicted that a therapeutic intervention into these pathogenetic mechanisms is a particular challange as it potentially interferes with those mechanisms that at the same time provide the basis for "higher brain function". © 2001 IBRO. Published by Elsevier Science Ltd. All rights reserved.

Key words: neurodegeneration, neuroplasticity, cell cycle, cellular differentiation, cell death, structural remodelling.

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*Tel.: +49-341-9725721; fax: +49-341-2114397.

E-mail address: aret@medizin.uni-leipzig.de (T. Arendt).

Abbreviations: Aβ, amyloid beta peptide; AchE, acetylcholinesterase; AD, Alzheimer's disease; ApoE, apolipoprotein E; APP, amyloid precursor protein; APLP, amyloid precursor-like protein; BDNF, brain-derived neurotrophic factor; BFGF, basic fibroblast growth factor; CAM, cell adhesion molecule; Cdk, cyclin-dependent kinase; CJD, Creutzfeldt–Jakob disease; CNTF, ciliary neurotrophic factor; ECL, lesion of the entorhinal cortex; EGF, epidermal growth factor; ERK, extracellular signal regulated kinase; FAD, familiar form of AD; FAK, focal adhesion kinase; GAP, growth-associated protein; GDP, guanosine diphosphate; GPI, glycosyl phosphatidyl inositol; GTP, guanosine triphosphate; HGF, hepatocyte growth factor; ICAM, intercellular adhesion molecule; IGF, insulin-like growth factor; IL, interleukin; INK4, inhibitors of cyclin-dependent kinase 4; JAM, junctional adhesion molecule; LCAM, liver cell adhesion molecule; LDL-R, low-density lipoprotein receptor; LRP, LDL-receptor-related protein; LTP, long-term potentiation; MAP, microtubule-associated protein; MAPK, mitogen-activated protein kinase; MAPKK, mitogen-activated protein kinase kinase; MARCKS, myristolated alanine-rich C-kinase substrate; NACP, non-A-beta-component precursor; NCAM, neural cell adhesion molecule; NGF, nerve growth factor; nNOS, nitric oxide synthase, neuronal isoform; PDGF, platelet-derived growth factor; PHF, paired helical filaments; PLD2, phospholipase D2; PrP, prion protein; PS, presenilin; PSA-NCAM, polysialylted neural cell adhesion molecule; SAM, substrate adhesion molecule; SNAP 25, synaptosomal-associated protein 25; TGF, transforming growth factor; TLN, telencephalin; TSE, tranmissible spongiform encephalopathy.

At the conclusion of the "Decade of the Brain" in 2000, the past presidents of the Society for Neuroscience drew up a list of what they considered the major advances that had occurred in neuroscience over the last decades. Among the seven major research achievements that were eventually listed based on a poll are the following five, directly related to neurodegeneration and neuronal plasticity:[368] (i) cloning of genes for familial Alzheimer's disease...; (ii) discovery of molecular bases of neural plasticity and of substances mediating new brain growth...; (iii) elucidation of the mechanisms underlying neuron death...; (iv) discovery that neurons can be induced to divide, and the detection of stem cells in the brain...; and (v) discovery of molecules for guidance of nerve fibres during development, leading to understanding of disorders in brain development and the potential of repair.

This résumé undoubtedly shows that in the last years major new insights have been achieved into cellular mechanisms of neurodegeneration and into the plastic potential of the brain that is retained throughout life. It makes clear, moreover, that neurodegenerative disorders such as Alzheimer's disease (AD) are not solely genetically determined. There are good reasons to assume that those mechanisms involved in processing of epigenetic information both during development and in the adult brain are at least equally involved in the disease.

It is the objective of the present paper to summarize evidence that it might be the disturbance of the structural brain self-organization which, based on both genetic and epigenetic information, constantly "creates" and "re-creates" the brain throughout life, that is the defect that underlies AD.

1. BASIC PRINCIPLES OF NERVOUS SYSTEM SELF-ORGANIZATION

1.1. The process of self-creation of the brain during development—genetic versus epigenetic information

The information contained in the structural organization of such a highly complex organ as the mammalian brain exceeds by far the information that can be stored in the genome.[703] Neurons are specified not only with respect to number and their position in the brain but also with respect to their interconnections. The high degree of freedom of theoretically possible interconnections becomes apparent when we assume that the number of neurons in the human brain amounts to about 10^{12} with each neuron receiving 10^4 to 10^5 synaptic contacts. The human genome consists of the comparatively small number of just 100,000 genes or even less (http://www.nhgri.nih.gov/HGP/). As connections between neurons, however, are by no means random but highly specific the question of structural specificity presents a particular problem.[186] This is even more so in higher mammals[379] and humans, where corticalization has led to an enormous increase in the number and interconnections of neurons, an increase that is far beyond the rather small evolutionary increase in the size of the genome.

As genetic instructions apparently are not sufficient to specify neuronal connectivity, algorithms of brain self-organization have been acquired that involve two epigenetic sources of information necessary to specify neuronal interconnections.[311,703,749,805]

During early development the information is provided by the micro-environment, mainly through biochemical signals, generated by local neurons and glial cells. Later on, when neurons become electrically excitable their

activity shapes their connectivity.[333,619,772] Self-organization of brain structure, however, cannot be based on spontaneously occurring activation pattern alone but requires sensory experience that allows for the extraction of the necessary additional epigenetic information.[232] The paradigm for thinking about how activity generates neuronal changes during development has been the work of David Hubel and Torsten Wiesel[334,335,801,802] on the effects of visual deprivation in cats and monkeys. Subsequent studies have confirmed and extended these findings, leading to the consensus that the primary role of activity in the development of the nervous system is to modulate (competitive) interactions among neurons.[118,271,521,687] The gradual brain enlargement during ontogenetic development is modulated by experience and regional growth is increased by locally augmented neural activity.[271,423,619,621,639,688,722,836] Neuronal activity is necessary not only for the initial establishment of specific connections but also for their maintenance[118] and rearrangement,[391] i.e. this "functional-self-creation plasticity process" of the brain is a lifelong process.[516]

1.2. Activity-dependent self-organization is a lifelong process

The wiring of the nervous system is highly variable from individual to individual and changes during the lifetime of each individual.[635] The degree of plasticity, and therefore the adaptive potency, may vary throughout the brain and may decline with increasing age. There are neuronal systems where these mechanisms of experience-dependent self-organization are limited to certain critical periods during brain development and where associations tend to be very stable once they are established. There are other brain areas, in particular cortical and limbic areas, where the function they subserve requires a lifelong structural remodelling. Brain structures involved in the regulation of "higher brain functions" such as learning, memory, perception, self-awareness and consciousness continously need to be reoptimized and self-adjusted. By this self-optimization process, the cognitive, behavioural and emotional reactivity of an individual is stepwise remodelled to meet the environmental demands.[338,339,355]

Mental function, thus, has as its cerebral basis a specific dynamic structure. It is the combination of flexible and rigid connections that the cerebral organization of mental activity is based upon.[287,351] While the presence of rigid connections ensures the stability of the principal characteristics of functions, the variable configuration of the flexible connections determines the unique, non-repeatable character of an experienced mental act.[351]

It was indeed shown recently that those neuronal systems playing a crucial role in "higher brain functions" and which, thus, become increasingly predominant as the evolutionary process of encephalization progresses,[274,326,789] such as hippocampus, neocortical association areas and the cholinergic basal forebrain neurons, retain a high degree of structural plasticity throughout life.[19–22,32] As these are exactly the same brain structures that display the highest degree of vulnerability during ageing and in AD,[19–22,32,84–86] a breakdown of mechanisms regulating modifications of synaptic connections as the basic process for the realization of "higher brain functions"[308] is, thus, likely to be critically involved in the pathomechanism of AD.

1.3. Failures are inherent in a system of dynamic stabilization

Whereas the basic wiring pattern of the mammalian nervous system is genetically programmed, its fine tuning throughout life is highly experience dependent.[611] The genome can only define the type of neurons capable of refitting connectivity throughout life and the rules according to which relations between phenomena in the outer world are evaluated and internalized through modifications of connectivity; it cannot, however, determine the specific kind of connection.[703]

The process of "selective stabilization of synapses" has been proposed by Jean-Pierre Changeux as a mechanism for the specification of neuronal networks during ontogeny and learning: "epigenesis exercises its selection on preformed synaptic networks. Learning is the stabilization of already established synaptic combinations and the elimination of others."[117]

Adaptive reorganization of neuronal connectivity which allows for the acquisition of new epigenetic information both during development and in the mature brain is thus based upon the strengthening of existing synapses, the formation of new synapses and the destabilization of previously established synaptic contacts. With the increasing need during evolution to organize brain structures of increasing complexity, these processes of dynamic stabilization and destabilization might become more and more important. At the same time, however, the delicate balance between stabilization and destabilization might also provide the basis for an increasing rate of failure. The effects of plasticity can, therefore, lead to either positive or negative changes. Thus, one can envisage of a spectrum of types of neuronal modifications that lead, at one end, to beneficial modifications as they may occur in learning and, at the other end, to detrimental effects as neurodegeneration and cell death.[113,260,468,508] This preservation of mechanisms of structural stabilization and labilization underlying a lifelong remodelling according to experience, with its increasing inherent possibilities of failure, not only may allow for the evolutionary aquisition of "higher brain function" but at the same time may provide the basis for a variety of neuropsychiatric disorders.

1.4. Structural reorganization of the adult brain

The idea that information could be stored by modifying interneuronal connections was originally proposed by Cajal.[628] He believed it probable that mental excercise led to greater growth of neuronal collaterals in the stimulated regions of the brain. (Cajal is quoted by Hebb as having advanced the "fantastic" idea that learning and memory are associated with amoeboid movements of synaptic endings.) Principles of sculpturing neuronal

connectivity closely follow rules of synaptic strengthening postulated by Hebb[312] which basically require a concerted activation of pre- and postsynaptic elements. He was proven right some 20 years later when an artificially induced modification of synaptic strength was first reported in the hippocampus.[69,70] This phenomenon of long-term potentiation is currently regarded as one of the best models of memory formation and has been shown recently to be associated with the formation of new synapses.[198,764]

This finding clearly shows that mechanisms of activity-dependent self-organization of brain structure are not confined to embryonic stages of development but similarly operate in post-natal life[703] and apparently also persist as a basic strategy in the adult brain.[98,380,478,586,635] There is good evidence to assume that the basic principles of this continuous restructuring of the brain in adulthood are the same as in brain maturation in early development.[145,146,199,473,618,779]

The work of Dale Purves has shown that ongoing changes in the nervous system and the variability of neuronal circuitry are not theoretical notions, but established fact.[620,622,623,640] Using the tools of electrophysiology and later optical techniques monitoring the living brain over time, he provided direct evidence that the nervous system is a structurally dynamic organ.[618] Applying a series of special microscopical techniques to living animals, he was able repeatedly to image individually identified neural elements in muscle,[451,472,638] autonomic ganglia,[608,620,622] surface epithelia such as the cornea[302] as well as the brain itself.[424,425,607,618] Using these methods, he could demonstrate that synaptic endings on mammalian skeletal muscle are remarkably stable[451] while synapses on the surface of autonomic ganglion cells observed over a period of several weeks change appreciably.[620,622] The most rapid remodelling that he was able to directly observe in the nervous system occurred in the mammalian eye, in which axons from sensory neurons in the trigeminal ganglion ramify near the surface of the cornea.[302] Substantial changes in terminal configuration occurred over periods as brief as a day.

Dendrites of identified neurons in the superior cervical ganglion of adult mice show slow and progressive changes in their higher order branches over periods of weeks to several months.[620] These changes produce an increase in the overall length and complexity of the dendritic arborization. When individual branches of the same neuron are followed over time, dendrites can be seen to extend, retract, disappear or form *de novo*. The net changes in dendritic length and complexity are accompanied by a continual reorganization of individual dendritic elements. As the majority of synapses in sympathetic ganglia occur on dendritic branches,[226] the remodelling of postsynaptic elements implies a substantial rearrangement of synaptic connections.

Direct evidence for spontaneously occurring synapse turnover has also been provided by the work of Townes-Anderson and Raviola.[767–769] In their ultrastructural studies of the parasympathetic innervation of the ciliary muscle of adult monkeys they found about 2% of the axonal profiles degenerating and a similar number regenerating.

1.5. Epigenetic information continously reshapes the brain

Basic experimental paradigms used to analyse how environmental epigenetic information is processed during brain maturation are sensory deprivation and enriched environmental conditions. Recent evidence indicates that these paradigms not only cause changes during developmental stages[282–284,367,377,378,400,545,647,652,704,705,792] but similarly induce long-lasting consequences if applied to adult organisms.[150,199,391,473,779]

Many representations of sensory stimuli in the neocortex are arranged as topographic maps. These cortical maps are not fixed, but show experience-dependent plasticity. Sensory deprivation, for example, causes the cortical area representing the deprived input to shrink, and the neighbouring spared representations to enlarge.[219,369,781,813] Representational sensory cortical maps are modifiable by manipulations of their sensory inputs throughout life indicating a constant restructuring by pattern of use.[98,188,380,447,586] This restructuring occurs not only under conditions of pathological disturbances, but also during the normal behavioural experiences of animals[359,632–634] and similarly affects somatosensory, auditory, visual and motor representations.[3,4,359,515,570,633,634,742,796]

Behavioural experience influences not only organization of sensory cortical representations but also the rate of neurogenesis derived from progenitor cells in the hippocampus,[52,392–395,779] a capability that is retained into adulthood in rodents,[8,393,394,420,459] non-human primates[277] and humans.[199] Neurons generated from progenitor cells migrate into the granule cell layer, differentiate, extend axons and express neuronal marker proteins.[109,385,386,581,725] In food-storing birds, storage and retrieval experiences are correlated with changes in hippocampal size and neurogenesis.[44,45,440,583] The increased size of the posterior hippocampi suggested to be involved in storage of spatial representations of the environment in birds has also been observed in humans engaged in occupations that require extensive navigation skills.[473]

These results clearly indicate that certain types of focused behavioural activity both during development and in the adult brain not only promote synaptic modification and synaptogensis[43,162,198,251,627,764] but can also influence neurogenesis and neuronal survival by controlling activation and progression of the cell cycle in the process of neuronal differentiation.[569,779,823]

Enriched environment in young[511,823] or even senescent rodents[395] results in persisting changes that dramatically reduce the rate of spontaneous apoptotic cell death later in life and protect against age-related decline of memory function. Social deprivation or stress, on the contrary, either during development[834] or in adult animals[240,276,277] is associated with an increased rate of apoptosis in the hippocampus and a reduced rate of neurogenesis in the adult animal. Early life events might, thus, prevent the brain from reaching complete levels of maturation and might predispose to a higher

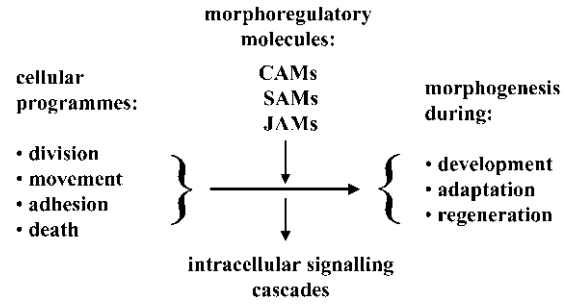

Fig. 1. The process of morphoregulation (according to the concept proposed by Edelman[192]) that regulates morphogenesis during development, adaptation and regeneration involves cellular programmes such as cell division, movement, adhesion and death and is controlled by *molecules*. The coordinated expression and function of these morphoregulatory molecules (CAMs: cell adhesion molecules; SAMs: substrate adhesion molecules; JAMs: cell junctional molecules) provide an essential link between genetic and epigenetic mechanisms. These molecules exert critical interactions at both the cell surface and the cytoskeleton and mediate their effects through activation of intracellular signalling cascades such as the p21ras/MAP-kinase pathway (see Fig. 6).

risk of neuropsychiatric disorders.[529,614] Those areas of the brain that take the longest to mature during childhood and adolescence are most vulnerable in AD,[86] and it has indeed been shown recently that the early-life childhood and adolescent environment is associated with the risk of AD.[529]

1.6. Molecular mechanisms that underlie structural plasticity

Mechanisms involved in structural adaptive plasticity, allowing for the constant re-adjustment of connectivity providing the basis for "higher brain function", are difficult to study and, therefore, are not very well understood. Attempts to develop an integrative theory of neuroplasticity have suggested that manifestations of plasticity as one of the essential characteristics of nervous tissue might have the same molecular basis, irrespective of the cause which triggered them,[771] and it has been proposed that no distinctions should be made between "developmental", "adaptive" or "restorative" plasticity.[803] It is, thus, reasonable to propose that reactive synaptic plasticity in the adult brain is only the massive manifestation of a normal potential of the nervous system and is based upon processes that are accelerated but basically identical to those involved in the natural turnover of synapses.[145,146,718]

Mechanisms underlying "higher brain functions" associated with long-term microstructural impacts of experience on the CNS that are very likely to require a lifelong high turnover of synapses might, therefore, involve the same molecules as "reactive synaptogenesis" as it occurs for example after a lesion of the entorhinal cortex (ECL)[171] such as (i) neurotrophic factors such as nerve growth factor (NGF),[135,152,294,721] brain-derived neurotrophic factor (BDNF),[224,294] insulin-like growth factor (IGF)-1,[387] ciliary neurotrophic factor (CNTF),[441] interleukin (IL)-1,[204] fibroblast growth factor (FGF)-2[205,266] or transforming growth factor (TGF)-beta 1;[417,534] (ii) several growth-associated proteins such as GAP-43;[53,452,486] (iii) neural cell adhesion molecules such as NCAM[375,522,737] and L1[374,738] and several synaptic proteins such as synaptophysin,[103,486] synapsin I,[514] NT75,[103] SNAP 25;[250,431] (iv) cellular lipids[602,603] and lipid carrier proteins such as apolipoprotein E;[601,602,604] and (v) changes in the expression[250,596,729] and subcellular distrubution[99,105,374] of microtubule-associated proteins and other cytoskeletal proteins.

1.7. Morphoregulatory molecules link genetic and epigenetic mechanisms

The process of morphogenesis during development, adaptation and regeneration is regulated by a process designated as "morphoregulation" by Gerald M. Edelman[192] (Fig. 1). Morphoregulation involves cellular programmes such as division, movement, adhesion and death and is controlled by *molecules*. According to the morphoregulator hypothesis,[192] an essential link between genetic and epigenetic mechanisms is provided by the coordinated expression and function of three families of morphoregulatory molecules:[189,191,193,194] cell adhesion molecules (CAMs), substrate adhesion molecules (SAMs) and cell junctional molecules (JAMs). These molecules exert critical interactions at both the cell surface and the cytoskeleton. Recent studies have supported the assumption of similar functions of these molecules during ontogenic development and neuronal plasticity in the adult brain.[799]

CAMs are single-pass transmembrane proteins that bind in a homophilic manner. The two main CAM families have as their prototypes the neural cell adhesion molecule (NCAM), homologous to the immunoglobulin superfamily[190] and the liver cell adhesion molecule (LCAM), which is homologous to the cadherins.[753] Behavioural tasks involving learning and memory function evoke subtile changes in the distribution pattern of NCAM,[182,556,649] with the highest accumulation of NCAM at the edges of synaptic active zone profiles.[706] Moreover, fragments of integrins or antibodies to NCAM or L1, another cell adhesion molecule of the immunoglobulin superfamily, interferes with long-term potentiation (LTP) *in vivo*.[11,42,182,466,646,669,726] Cadherins are involved in synapse formation both during development[207] and in the adult.[48,124,125,773]

The SAMs are mainly extracellular matrix proteins secreted by cells such as fibronectin, laminin, collagen, cytotactin and various proteoglycans.[811] The JAMs form tight junctions, adherent junctions and desmosomes after initial cell adhesion mediated by CAMs.[512] The combinatory possibilities of interactions between morphoregulatory molecules are enormous, some CAMs have domains homologous to those of SAMs and CAMs may also be part of intercellular junctions. This dynamic set of interactions allows these molecules to bind and link cells transiently.

Axonal and dendritic plasticity requires tuned changes at both the neuronal surface and the cellular interior. Through regulating cell adhesion, morphoregulatory molecules might be involved in relaying signals to the

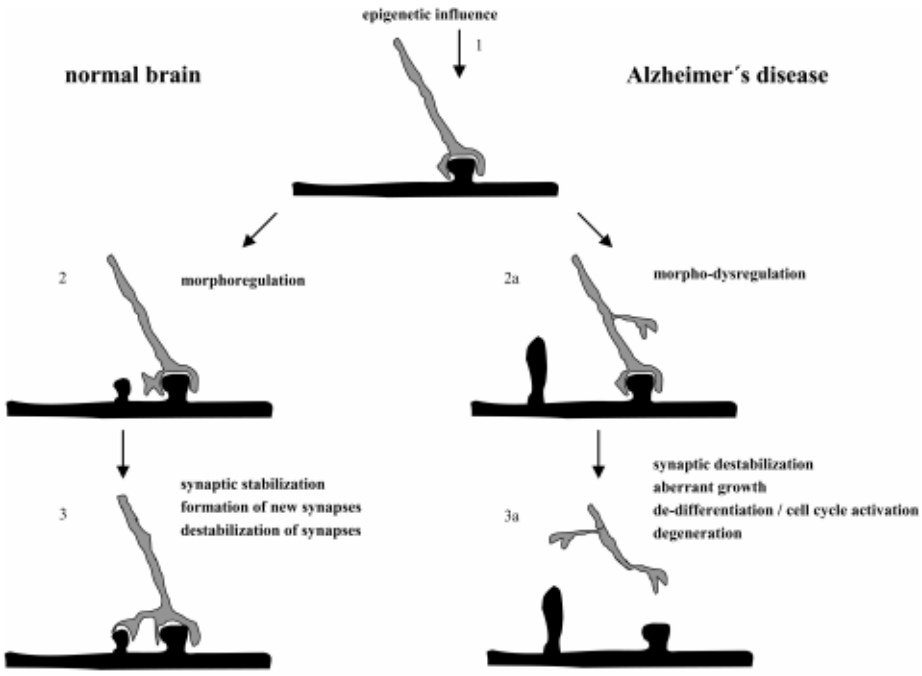

Fig. 2. Brain areas affected by AD pathology are those structures involved in the regulation of "higher brain functions" that become increasingly predominant as the evolutionary process of encephalization progresses, such as hippocampus, neocortical association areas and the cholinergic basal forebrain neurons. The functions these areas subserve such as learning, memory, perception, self-awareness and consciousness require a lifelong refitting of synaptic contacts that allows for the aquisition of new epigenetic information (1). This adaptive reorganization of neuronal connectivity in the mature brain is mediated by the process of morphoregulation (2) and results in the strengthening of existing synapses, the formation of new synapses and the destabilization of previously established synaptic contacts (3). With the increasing need during evolution to organize brain structures of increasing complexity, these processes of dynamic stabilization and destabilization become more and more important but might also provide the basis for an increasing rate of failure. It is proposed that it is this particularly high plastic ability of a subset of neurons in the adult brain that allows for ongoing morphoregulatory processes after development is completed but at the same time renders these neurons particularly vulnerable. Morpho-dysregulation in AD (2a), accompanied by an aberrant activation of intracellular mitogenic signalling might, thus, be a slowly progressing dysfunction that eventually overrides the differentiation control and results in synaptic destabilization, aberrant growth and dedifferentiation, a condition that is in conflict with the otherwise "mature" background of the nervous system (3a) and, thus, ultimately results in cell death.

cell interior, thereby controlling primary cellular processes such as cell division, movement and differentiation.[270,799] Cell surface modulation events can alter the mobility of transmembrane proteins via changes in cytoskeletal states and is correlated with inhibition of mitogenesis.[187] Adhesion molecules might also form a direct part of intracellular signalling cascades regulating cell proliferation and differentiation.[288,415,513,530,675,676] Integrins and NCAMs are coupled to intracellular signal transduction pathways via focal adhesion kinases (FAK) and the ras-dependent mitogen activated protein kinase cascade,[298,404,575,582,668] which both are implicated in the pathomechanism of AD.[238,239,699,832,833]

2. ALZHEIMER'S DISEASE AS A DISORDER OF BRAIN SELF-ORGANIZATION AND MORPHOREGULATION

There are numerous indications of alterations of neuroplasticity in AD and the idea that aberrant plasticity, i.e. abnormal sprouting or a regenerative failure, is critically involved in the pathomechanism of AD has repeatedly been suggested.[40,101,142,176,177,222,246,406,517,527,565,594,642,745,793]

We propose that it might not just be the ability of the brain to react to some age-related or otherwise undefined structural disturbance, but rather that it is its *ability to modify its own structural organization* and functioning as an adaptive response to functional demands,[409,803] (i.e. the structural potential that "creates" the brain), which is impaired in AD (Fig. 2).

Based on this hypothesis several testable predictions can be formulated:

1. AD is a synaptic disorder.
2. AD is associated with aberrant sprouting at both the presynaptic (axonal) and postsynaptic (dendritic) site.
3. The spatial and temporal distribution of AD pathology follows the pattern of structural neuroplasticity in adulthood, which is a developmental pattern.
4. AD pathology preferentially involves molecules critical for the regulation of modifications of synaptic connections, i.e. "morphoregulatory" molecules that are developmentally regulated, such as growth-inducing and growth-associated molecules, synaptic molecules, adhesion molecules, molecules involved in membrane turnover, cytoskeletal proteins, etc.
5. Life events that place an additional burden on the plastic capacity of the brain or that require a particularly high plastic capacity of the brain might trigger the onset of the disease or might stimulate a more rapid progression of the disease. In other words,

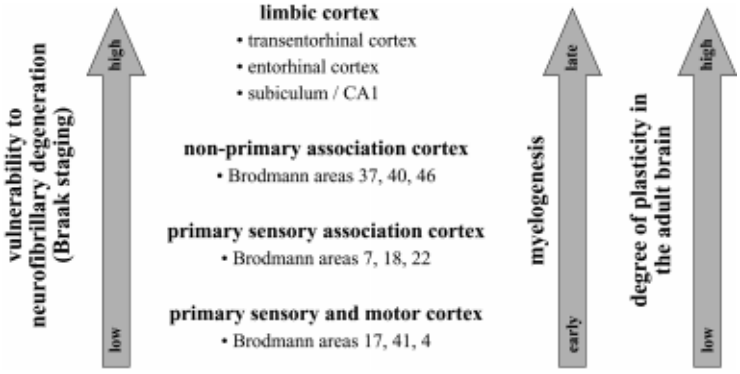

Fig. 3. The distribution of vulnerable neurons in AD matches the pattern of late ontogenetic development and a high neuroplastic potential in the mature brain. Those neuronal systems playing a crucial role in "higher brain functions" and, thus, become increasingly predominant as the evolutionary process of encephalization progresses such as hippocampus and neocortical association areas retain a high degree of structural plasticity throughout life. These areas of the brain take the longest to mature during childhood and adolescence. Exactly the same brain structures display the highest degree of vulnerability during ageing and in AD. (Modified after Refs 22, 85 and 86.)

they might increase the risk for AD in the sense that they determine when, not whether one gets AD.

6. AD is associated with a reactivation of developmental programmes that are incompatible with a differentiated cellular background and, therefore, lead to neuronal death.

If the hypothesis is correct, it can be predicted, furthermore, that a therapeutic intervention into these pathogenetic mechanisms might be particularly difficult as it potentially interferes with those mechanisms that at the same time provide the basis for "higher brain function".

Predictions 1 to 3 have been proven right (Fig. 3 and Section 2.2);[19–22,32] the same holds true for prediction 5. All risk factors for AD, particularly those related to life events, such as early-life childhood and adolescent environment,[529] psychosocial and mental inactivity, loss of motivation and mental stress,[47,243,405,712] a lower level of education and/or occupation,[65,73,107,172,543,576,727,728,800] higher age,[244,373] exposure to neurotoxic factors,[230,421,454,661,674,713] brain injury[510,544,630,641] or known risk factors for vascular disease also relevant to AD such as high blood pressure,[435,707,746] low blood levels of folate and vitamin B_{12} and elevated total homocysteine levels,[126] might be associated either with a lower capacity of plastic adaptability or with an additional burden placed on the system of structural adaptation. This assumption, either that a pathological predisposition might lower the critical threshold of decompensation or that some additional force might override this threshold, is in agreement with the previous suggestion[126,364] that some kind of "insult" may trigger the onset of AD. Similarly, the genetic risk factor ApoE 4 allel has recently been shown to predict "when not whether" susceptible individuals will develop AD.[518] Genetic aetiologies such as mutations in the genes for APP or presenilins might also be related to alterations in the normal plastic capacity of the brain (see Section 2.1).

With respect to prediction 4 observations might be relevant indicating that a partial ontogenetic regression occurs in AD that involves reactivation of developmental programmes including abortive mitosis that eventually results in cell death as they are in conflict with the otherwise "mature" background of the nervous system (see Section 2.3).

2.1. Morphoregulatory molecules in Alzheimer's disease and other neurodegenerative disorders

A disturbance of brain self-organization that becomes manifested in the adult brain might involve morphoregulatory molecules, i.e molecules that are developmentally regulated and are expressed in the adult brain mainly in areas that retain a high neuroplastic potential. According to the necessity of synaptic turnover and reorganization, growth cone and synaptic properties might overlap to some degree and the preservation of these properties might allow for synaptic plasticity in the adult brain.[593] One notable candidate involved in these processes is GAP-43 that persists in neocortical association areas and in the limbic system throughout life, where the protein might play an important role in mediating experience-dependent plasticity.[54]

Recent studies demonstrate alterations of different cellular and substrate adhesive molecules, their ligands and other morphoregulatory molecules in AD. The presence, for example, of GAP-43, heparan sulfate, laminin, NCAM, various cytokines and neurotrophic factors in neuritic plaques (see Table 1) might be an indication of tissue remodelling.

There is a growing body of evidence, moreover, that the amyloid precursor protein (APP), presenilins, alpha-synuclein, prion protein (PrP) and apolipoprotein E (ApoE) critically involved in the pathology of AD, Parkinson's disease, Lewy body dementia, Creutzfeldt–Jacob disease and other neurodegenerative disorders, are in fact morphoregulatory molecules playing a role in formation, turnover and stabilization of synapses both during development and in the adult brain. All these molecules are developmentally regulated and are expressed in the adult brain only in areas that retain a high neuroplastic capacity. They share molecular

Table 1. Indication of dendritic and axonal sprouting in Alzheimer's disease

Dendritic sprouting
Somatodendritic sprouts (filopodium-like processes that resemble growth cones) occur on both cortical and subcortical neurons
MAP2 and tau are co-localized in these growth structures which **recapitulates** their co-distribution in **developing neurites**
References: 37, 214, 345, 470, 585, 667
Axonal sprouting
Axonal sprouts present as abundant coiled fibres and dystrophic neurites in association with plaques contain GAP-43 and synaptophysin
Spine density of the granular cell dendrites is significantly reduced in distal parts of the dendrites while it remains unaltered in most proximal parts which might indicate **collateral sprouting of undamaged inputs**
AChE innervation pattern in the terminal zone of the perforant pathway in AD indicates **compensatory septal afferent sprouting** in the hippocampus
Expansion of kainic acid receptor distribution in AD hippocampus matches the pattern of receptor spreading observed in rats after **axon sprouting of commissural and associational fibres** into the denervated molecular layer of the dentate gyrus induced by lesions of the entorhinal cortex
References: 248, 256, 342, 497
Tangle-bearing neurons and dystrophic neurites contain growth-associated proteins
GAP-43
Thy-1
Collagen IV
Laminin
Integrin receptor VLA6
Heparin binding growth-associated molecule (HB-GAM)
Transforming growth factor (TGF)-beta 2
Neuronal growth-associated protein SCG10
Spectrin
N and C termini of amyloid precursor protein (APP)
References: 221, 443, 482, 489, 496, 498, 574, 702, 806, 831
Growth-promoting factors and their receptors are increased in plaques
S100 beta
Basic fibroblast growth factor (bFGF)
Hepatocyte growth factor (HGF/SF)
Platelet-derived growth factor (PDGF)-BB
TrkA and TrkB receptors
Proteoglycans:
heparan sulfate
keratan sulfate
deramatan sulfate
chondroitin sulfate
Epidermal growth factor receptor (EGF-R)
Intercellular cell adhesion molecule ICAM-1
Integrins
Collagen
Laminin
Telencephalin
References: 67, 137, 178, 195, 210, 234, 265, 323, 492, 557, 689, 711, 784
Synaptic proteins are enriched in plaques
Chromogranin A
Chromogranin C/secretoneurin
SNAP 25
Synaptophysin
Synaptotagmin
NT75
Spectrin
References: 103, 216, 280, 389, 434, 490, 780, 790, 795

properties of classical CAMs or directly interact with them and have similar distributions as CAMs or growth-associated proteins (GAPs)[144,566,733,734] (see Tables 2–6).

2.1.1. Classical morphoregulatory molecules. While the number of NCAM-expressing neurons is reduced in AD,[821] the highly polysialylated form (PSA-NCAM), a developmentally regulated molecule involved in neurite growth, synaptogenesis and structural remodelling[151,553,645,680] and expressed in the adult brain only in areas that retain a neuroplastic potential, is

Table 2. Involvement of ß-amyloid precursor protein in synaptic plasticity and morphoregulation

Synaptic localization and role in cell adhesion

APP undergoes **fast axonal transport** to synaptic sites
APP (and its homologue APLP) is preferentially localized to **presynaptic membranes**
APP co-localizes with **adhesion patch components** on the surface of cortical neurons in primary culture
Cell-surface APP co-localizes with **beta 1 integrins** at substrate contact sites in neural cells, a C-terminal APP fragment promotes cell adhesion in an integrin-like mode
APP is a substrate for **transglutaminase** involved in synapse stabilization by cross-linking large, multidomain extracellular glycoproteins
APP homologue APLP2 contributes to **epithelial cell adhesion**
Down-regulation of APP by antisense oligonucleotides reduces **neuronal adhesion** to specific substrates
APP isoforms contain extracelluar domains for **binding of glycosaminoglycans and collagen**
Appican, the chondroitin sulfate proteoglycan form of APP promotes **cell adhesion** to extracellular matrix
Transgenic *Drosophila* expressing human APP show a **blistered-wing phenotype**
References: 88, 102, 147, 227, 258, 325, 376, 398, 411, 448, 554, 578, 637, 659, 671, 672, 694, 697, 700, 733, 762, 811, 816

Synaptotrophic effects/induction of sprouting

APP (and their homologue APLP) is **developmentally expressed**, peaks during periods of neuronal differentiation and synaptogenesis *in vivo* and *in vitro*; beta APP695 increases selectively and progressively during neuronal **differentiation**
APP is localized in **growing neurites** of neonatal rat brain
In mammals, transmembrane APP is associated with **elongating axons**, whereas secreted APP is correlated with **synaptogensis**
Differentiation of neurons is accompanied by increased **ßAPP695** expression and membrane retention of the protein as intact, full-length molecules
Drosophila APPL is enriched in growing axons and areas of synapse formation, overexpression of *Drosophila* APPL promotes **synapse differentiation** and increases the number of synaptic boutons at the neuromuscular junction
APP induces functional **synapse maturation** *in vitro* (spontaneous oscillations of intracellular Ca^{2+} concentration)
sAPP regulates spontaneous and impulse-evoked postsynaptic currents on **developing synapses** *in vitro*
Hippocampal neurons *in vitro* from APP-deficient mice show diminished viability and **retarded axon growth**, dendrite branching, and dendrite numbers
Neuronal overexpression of human APP in transgenic mice induces expression of **synaptophysin and GAP-43**
Entorhinal axons in transgenic mice (APP23 mice, Swedish double mutation) form **dystrophic GAP-43-immunopositive axonal terminals** around amyloid plaques as well as surrounding vascular amyloid in ectopic locations within the hippocampus, the thalamus, white matter tracts
APP is localized in **GAP43-immunoreactive outgrowing neurites** of neonatal rat brain as well as in GAP43-immunoreactive aberrant sprouting neurites in AD
APP-null mice develop profound loss of immunoreactivities for the **presynaptic terminal vesicle marker proteins** synaptophysin and synapsin, reduction of dendritic length of CA1 neurons
Administration of an APP17mer increases the **number of presynaptic terminals** in rat brain and attenuates the neuronal dysfunction induced by ischaemia in rabbit brain
Administration of sAPP counteracts the inhibitory effect of glutamate on **dendrite outgrowth** in cultured embryonic hippocampal neurons
Administration of APP with the Kunitz insert *in vitro* induces **axonal sprouting**
sAPP enhances **proliferation of neural stem cells** from fetal rat brain
APP is a mediator of the effects of nerve growth factor on **neurite outgrowth**; APP is involved in NGF-mediated trophic signalling; antibodies to APP or APP antisense oligonucleotides diminish NGF-induced increases in **cellular size, neurite length and branching** in PC12 cells
Neurite outgrowth promoting effects of APP are mediated via interaction with a developmentally regulated HSPG
References: 9, 10, 82, 91, 127, 149, 163, 206, 235, 310, 341, 363, 398, 402, 410, 458, 460, 475, 496, 498, 509, 526, 531, 536, 537, 547–550, 571, 572, 589, 597, 626, 643, 655, 679, 708, 734, 765, 766, 770, 804, 822

Regulation of synaptic plasticity associated with LTP and learning

APP-null mice and transgenic mice with APP mutations show impaired **LTP** associated with impaired **cognitive performance**
sAPP shifts the frequency dependency for induction of **LTD** and enhances LTP in hippocampal slices
Administration of Aß alters **LTP** both *in vitro* and *in vivo*
Intraventricular infusion of antibodies to APP impair passive avoidance **learning**
Synaptic APP increase with **learning** capacity in rats
Administration of an APP17mer to rat brain increases **memory retention**
References: 119, 154, 163, 181, 336, 348, 426, 432, 551, 563, 643, 679, 761, 810, 837

Up-regulation in response to synapse loss

APP is up-regulated in response to **traumatic brain injury**/experimental brain lesion
Soluble Aβ in AD inversely correlates with **synapse loss**
References: 252, 462, 735, 778

over-expressed in AD.[520] The intercellular adhesion molecule-1 (ICAM-1) is also increased and is mainly enriched in senile plaques.[6,783] Expression of telencephalin (TLN), a cell adhesion molecule of the immunoglobulin superfamily that is developmentally expressed in the telencephalon of the mammalian CNS during dendritic elongation and synaptogenesis,[535] on the contrary, is markedly decreased in the brain of AD patients.[323]

2.1.2. Acetylcholinesterase. Apart from its catalytic function in hydrolysing acetylcholine, acetylcholinesterase (AChE) affects cell proliferation, differentiation and

Table 3. Involvement of presenilin 1 in synaptic plasticity and morphoregulation

Synaptic localization and role in cell adhesion
Presenilin concentrates at **synaptic sites** in the brain and **intercellular contacts** in epithelial tissue (proteolytic fragments of presenilin 1 are present in synaptic plasma membranes, neurite growth cone membranes, and small synaptic vesicles of rat brain)
Presenilin forms complexes with the cadherin/catenin cell–cell adhesion system
Presenilin overexpression in human kidney cells **enhances cell–cell adhesion**
Endogenous PS1 redistributes to the surface of lamellipodia upon **adhesion** of Jurkat cells to a collagen matrix
In COS-7cells overexpressing PS1, PS1 immunoreactivity is concentrated on the surface at **cell–cell-contact sites**
References: 50, 253, 383, 637, 677, 751, 752, 794, 824
Developmental regulation of expression
Developmental expression of presenilin shows two **peaks**, one during late embryogenesis paralleling the pattern previously reported for Notch, suggesting an involvement in **neurogenesis** and skeleton formation and a second during postnatal development when proliferation and migration are still ongoing, suggesting an involvement in **differentiation** and **synaptogenesis**
Presenilin null mice exhibit early **embryonic patterning defects**
Presenilin processing is **developmentally regulated** and an alternative pathway of PS1 proteolytic processing is induced in the brain by neuronal **differentiation**
References: 58, 110, 179, 206, 303, 304, 532, 754, 777, 809
Notch signalling—regulation of cell differentiation, proliferation
The presenilin homologue sel-12 in *Caenorhabditis elegans* facilitates lin-12 function, the mammalian homologue thereof is Notch1, a transmembrane receptor involved in regulation of **cell differentiation, proliferation and programmed cell death**
Presenilins show specific physical **interaction with Notch1**
Notch1 inhibits **neurite outgrowth** in postmitotic primary neurons, an effect that is markedly attenuated in neurons from PS1 knockout mice, and enhanced in neurons from transgenic mice overexpressing wild-type PS1, but not mutant PS1
Mutations in *Drosophila* presenilin (Dps) genetically interact with Notch and result in an early pupal-lethal phenotype characterized by defects in eye and wing development and incomplete **neuronal differentiation** within the larval CNS
PS1-deficient mice develop **cortical dysplasia**
References: 55, 56, 292, 304, 445, 519, 631
Regulation of neurite outgrowth
Overexpression of wild-type PS1 gene in mouse neuroblastoma (N2a) cell lines stimulates **neuritic outgrowths** accompanied by accumulation of PS1 immunoreactivity in neurites; this effect is disturbed in FAD-linked PS1 mutations (P117L, M146L)
Expression of AD-linked human PS-1 mutation (L286V) in PC12 cells results in aberrant **differentiation** responses to nerve growth factor (NGF)
References: 180, 236
Involvement in synaptic plasticity associated with LTP
Transgenic mice carrying FAD-linked PS1-mutation show **alterations in LTP**
References: 580, 827
Synaptic dysfunction in FAD-linked PS1-mutation
PS1 mutant mice show altered calcium homeostasis and mitochondrial dysfunction in cortical **synaptic compartments**
Reference: 49

responses to various insults, including stress. While "synaptic" AChE-S constitutes the principal multimeric enzyme in brain and muscle; soluble, monomeric "read-through" AChE-R appears in embryonic and tumour cells and is induced under psychological, chemical and physical stress.[289] The homology of AChE to the cell adhesion proteins, gliotactin, glutactin and the neurexins, which have more established functions in nervous system development, might be the basis of its morphogenetic functions.[289,437]

AChE associated with the pathological lesions of AD possesses different enzymatic properties to synaptic AChE[257] with some resemblance to the embryonic enzyme,[23] making a morphogenetic "neo-embryonic"[437] function involved in induction of aberrant growth of neuronal processes likely.

2.1.3. Amyloid precursor protein. The amyloid protein precursor (APP) gene is part of a multigene superfamily from which 16 homologous amyloid precursor-like proteins (APLP) and APP species homologues have been isolated and characterized. APP is a type I integral membrane protein homologue to glycosylated membrane receptors[384] present on the surface of neurons and glia.[89,700,816] It is processed by proteases referred to as "secretases" into soluble APP fragments and Aβ, the major component of senile plaques in AD.[384] APP is developmentally expressed,[213,547] is highly abundant at synaptic sites and is released under conditions of LTP.[209]

Although the precise physiological function of APP is still unclear, both cellular APP and secreted forms have been implicated in the modulation of differentiation,

Table 4. Involvement of α-synuclein in synaptic plasticity and morphoregulation

Synaptic localization
α-Synuclein is axonally transported by all rate components and is localized to **presynaptic membranes** and synaptic vesicles
In the adult brain, expression of α-synuclein is highest in **brain regions**, involved in **ongoing experience-dependent modifications** such as hippocampus, olfactory bulb, amygdala
References: 346, 352, 360, 479, 480, 491, 562, 693
Developmental regulation of expression
Expression of synucleins is developmentally regulated and peaks during **synaptogenesis** and neural **differentiation**
The ratio α-synuclein/synaptophysin (i.e. the α-synuclein content per synapse) is particularly high during **synaptogenesis**
References: 307, 331, 352, 590, 807
Involvement in regulation of cell differentiation
α-Synuclein expression is up-regulated during phorbol ester-induced megakaryocytic **differentiation**, while ß-synuclein is down-regulated
α-Synuclein is widely distributed in **brain tumours** showing neuronal differentiation, predictor of tumour progression
Synucleins are involved in spermatogonia where expression coincides with **meiosis**
References: 307, 390, 692
Involvement in neuronal regeneration and structural plasticity
α-Synuclein is highly expressed in olfactory receptor neurons (ORNs) of the olfactory epithelium that **regenerates** throughout the lifespan
Reference: 184
Involvement in synaptic pathology
A fragment of α-synuclein, the **non-A beta component of AD amyloid** (NAC), is highly co-localized with synaptophysin-immunoreactive structures (presynaptic terminals)
The ratio α-synuclein/synaptophysin (i.e. the α-synuclein **content per synapse)** is doubled in AD
Degenerative terminals of the perforant pathway in patients with PD, diffuse Lewy body disease and dystrophic neuritic processes in mixed DLB/AD cases are α-synuclein immunoreactive
Expression of rat synuclein in the substantia nigra pars compacta is up-regulated in a rodent model of **apoptotic death** induced by developmental injury to their target, the striatum
References: 155, 241, 347, 397, 491, 774
Involvement in learning-associated synaptic plasticity
α-Synuclein expression is altered during the critical period of **song learning in birds**
Reference: 255

growth and connectivity of neurites[7,438,475,526,589,626,654,670] (see Table 2).

Comparison of exon structure (including the uncharacterized APL-1 gene), construction of phylogenetic trees, and analysis of the protein sequence alignment of known homologues of the APP superfamily were performed to reconstruct the evolution of the family and to assess the functional significance of conserved protein sequences between homologues. This analysis supports a cell adhesion function for all members of the APP superfamily, with specificity determined by those sequences that are not conserved between APLP lineages, and provides evidence for an increasingly complex APP superfamily during evolution. The analysis also suggests that *Drosophila* APPL and *Caenorhabditis elegans* APL-1 may be a fourth APLP lineage indicating that these proteins, while not functional homologues of human APP, are similarly likely to regulate cell adhesion.[147,148] Recent evidence suggests that accumulation of Aβ may disrupt cell-adhesion mechanisms *in vivo*.[612,650]

2.1.4. Presenilins. Presenilin 1 (PS1) is a transmembrane protein with eight transmembrane domains expressed in many tissues including the brain where it is enriched in neurons.[157,196,449,691] Presenilins influence the functions of different cell adhesion molecules either directly or indirectly (see Table 3). PS1 binds members of the armadillo family of proteins including δ- and β-catenin[824,838] and promotes processing and signalling of Notch1 receptor, suggesting a role in development.[175,736,820] Notch is a neurite outgrowth promoting cell surface glycoprotein with EGF-like repeats, characteristic of many cell adhesion molecules, that may only reach the cell surface in the presence of presenilins.[166,631,736,820]

Notch-ligand interactions are a phylogenetically highly conserved process that mediates cell–cell-communication and regulates cell proliferation and differentiation.[38,39,285,519,525,625] At least in some cells, Notch-1 signalling affects cell-cycle progression and might, thus, be involved in neuronal plasticity[5] and in regulating the balance between proliferation and differentiation.[112,167] Mechanisms of cell fate determination by Notch-dependent signalling may involve key signalling molecules such as p53, ras and myc family members.[519]

Presenilin 1 and 2 are mutated in the majority of

Table 5. Involvement of the cellular prion protein PrPc in synaptic plasticity and morphoregulation

Synaptic localization
PrPc is predominantly localized to **presynaptic membranes** PrPc is particularly abundant in synaptic terminal fields in **brain regions** involved in **ongoing experience-dependent modifications** such as olfactory bulb, limbic-associated structures References: 228, 264, 316, 656, 755
Neurotrophic action
Intracerebral inoculation of Sc237 scrapie in hamsters results in increase **branching of basal dendrites** of hippocampal CA1 pyramidal cells Reference: 46
Influence on neuronal connectivity
PrP null mice show abnormal **mossy fibre reorganization** in the hippocampus Reference: 133
Influence on LTP and learning/memory
Hamsters intracerebrally inoculated with Sc237 scrapie or mice infected with ME7 scrapie show impaired **LTP** PrP null mice show disturbed **long-term memory** References: 46, 134, 365, 567
Synaptic pathology is the primary neuropathological feature of spongiform encephalopathy
Synaptic markers (synaptophysin, synapsin-I, SNAP-25, syntaxin-I) are reduced early in the course of sporadic CJD PrPsc is preferentially found in the **presynaptic domain** of synapses in CJD, Gerstmann–Sträussler–Scheinker disease (GSS), kuru and bovine spongiform encephalopathy **Synaptic degeneration** is an early event in CJD and in a panencephalitic model of CJD (Echigo-1 strain) References: 96, 131, 217, 286, 295, 328, 399, 450, 506, 579, 644, 715, 756, 797, 815

familial, early-onset AD cases.[413,636] Patients with sporadic AD show increased Notch1 expression in the hippocampus.[57] It remains unknown at present whether this may represent an accumulation of incorrectly processed or targeted protein, or a compensatory mechanism.

Classical cadherins, including E- and N-cadherin, are a family of cell surface single-pass transmembrane proteins that control critical events in cell–cell adhesion, recognition and tissue development. Cadherin-based junctions are specialized forms of cellular adhesive contacts at which plasmalemmal classical cadherins form complexes with cytosolic catenins linked to the cortical actin cytoskeleton. Cadherins and associated catenins are found in synaptic junctions, where they are thought to link pre- and postsynaptic membranes.[775] Recent reports provide evidence that PS1 is localized at cell–cell adhesion sites and forms complexes with components of the cadherin/catenin adhesion system, suggesting a function for PS1 in cell–cell adhesion.[253,555,824,835,838] FAD-mutant PS1 expression decreases the stability and/or enhances the degradation of beta-catenin.[383,794]

2.1.5. Synucleins. Synucleins comprise a family of closely related proteins, especially abundant in neural tissue, where they are particularly enriched in presynaptic terminals.[479] The synucleins were originally identified independently as being involved in vesicle-associated processes in the *Torpedo* electrical organ,[479] as developmentally regulated proteins related to song learning in birds[255] and as a phosphoprotein (PNP-14) in mammalian brain.[562]

Alpha-synuclein, particularly enriched in the telencephalon,[346,352] has been identified as the primary component of Lewy bodies[720,791] that might also contain other synaptic proteins.[790] In AD, a central 35-residue fragment of alpha-synuclein, orginally being referred to as "the non-A-beta-component precursor" (NACP), is a major component of amyloid plaques where it comprises about 10% of all protein components.[491,774] In early AD, alpha-synuclein appears to be elevated both in the cytosol[353] and at individual synaptic sites.[491] A rare form of inherited Parkinson's disease is linked to a mutation in the alpha-synuclein gene.[606]

The physiological function of alpha-synuclein remains unknown (see Table 4). Its structure is highly conserved among vertebrates and resembles those of apolipoproteins.[128] In the CNS alpha-synuclein appears to be localized almost exclusively to presynaptic terminals.[346,354] Its structure and subcellular localization indicate that it may be capable of interacting transiently or reversibly with phospholipid membranes.[129] Alpha-synuclein undergoes a massive conformational shift in the presence of acidic phospholipids.[158] It is also a highly specific inhibitor of phospholipase D2 (PLD2)[356] which produces phosphatidic acid by hydrolysis of phosphatidylcholine.[203] These mechanisms might be involved in the regulation of cleavage of membrane lipids and might, thus, be highly relevant to membrane biogenesis and turnover.[129] Cellular injection of PLD2, for example, provokes cytoskeletal reorganization and production of filopodia.[132] This potential involvement in membrane turnover might also be relevant to its function in non-neuronal

Table 6. Involvement of apolipoprotein E in neuronal plasticity and morphoregulation

Developmental regulation of expression and secretion
ApoE and its main receptor in brain, the alpha-2-macroglobulin/low-density lipoprotein receptor-related protein, are transiently highly expressed in embryonic development during **morphogenesis**
References: 41, 460, 798
Neurotrophic effects/induction of sprouting
ApoE stimulates **neurite growth** on primary neuronal cultures, neurite growth-promoting effects are isoform specific: ApoE3 > ApoE4
Synaptic densities of cholinergic, noradrenergic and serotonergic projections in specific brain regions of apoE-deficient mice are markedly lower than those of controls
Cultures derived from ApoE-knockout mice are defective in **neuronal sprouting**, transgenes restore sprouting isoform specific: ApoE3 > ApoE4
The enhancement of **synaptic sprouting** by estradiol (E2) in response to entorhinal cortex (EC) lesion operates via an apolipoprotein E (ApoE)-dependent mechanism
References: 120, 297, 564, 624, 731, 758, 759
Effects on cell cycle
ApoE inhibits the **proliferation** of several cell types, including endothelial cells, human melanoma cells, interleukin-dependent lymphocytes and human breast carcinoma cells in a dose- and time-dependent manner
ApoE inhibits the **proliferation** of growth factor-responsive cells by blockade in the **G1 phas**e of the cell cycle
Apo E inhibits platelet-derived growth factor-induced vascular smooth muscle cell migration and **proliferation** by suppressing signal transduction and preventing cell entry to **G1 phase**
Antiproliferative effects of ApoE involve alterations of cell-matrix interactions and have been correlated with significant reductions in agonist-stimulated **MAP-kinase** activity and **cyclin D1** expression
References: 350, 528, 577, 788
LTP/memory function
The low-density lipoprotein receptor-related protein, the main ApoE receptor in brain is involved in hippocampal **LTP**
ApoE-deficient mice show alterations in **LTP** and **cognitive dysfunction**
Alpha-2-macroglobulin (a ligand of the ApoE receptor) inhibits **LTP**
Cognitive impairment in ApoE-deficient mice is ameliorated by infusion of recombinant ApoE
ApoE antibodies affect the retention of **passive avoidance memory** in the chick
References: 115, 272, 278, 418, 419, 427, 502, 573, 782, 839
Involvement in the repair response to tissue injury
Apo E markedly increases at sites of injury and **regeneration** in the peripheral and central nervous system
ApoE may play an isoform-specific role in determining both the initial response and the subsequent consequences to acute **brain injury**
ApoE can interact with **growth regulatory factors** such as CNTF, heparin, laminin and proteoglycans
References: 197, 279, 293, 332, 343, 344, 474, 828

cells where it has been implicated, for example, in breast cancer progression.[361] The expression of synucleins is developmentally regulated with a selective up-regulation of alpha-synuclein during cellular differentiation.[307]

One of the best characterized model systems where alpha-synuclein is involved, is the avian song control system.[254] In this system it is highly enriched in synapses during the early period of learning[362] when synapses undergo a large physical change in their organization with a reduction in their numbers by half accompanied by a doubling in size of remaining synapses.[317] Based on this evidence, the hypothesis has been put forward[129] that synuclein is involved in localized, experience-dependent turnover of synaptic membranes, a process important for "synaptic tagging",[233] providing the basis for lifelong learning and memory formation.

2.1.6. Prion protein. The prion protein (PrP^C, the normal, cellular isoform) is a cell surface sialo-glycoprotein with a glycosyl-phosphatidyl-inositol (GPI) domain permitting attachment to cell membranes, present in a number of tissues including brain.[51,72,79,114,723,724] An anomalous, protease-resistant form (PrP^{Sc}) accumulates in brain during transmissible spongiform encephalopathies (TSE) such as Creutzfeldt–Jakob disease, scrapie and bovine spongiform encephalopathy, which has led to the hypothesis that this protein is the infectious agent in these diseases.[616]

Although due to this involvement in TSE, the PrP has been of considerable interest, its function in the normal brain is unknown (see Table 5). The cellular form of PrP is attached to the cell surface by a GPI anchor.[78] In neurons, newly synthesized PrP is anterogradely transported to the synaptic terminal.[77] PrP is enriched at many limbic brain structures, such as hippocampus, ventral pallidum, olfactory bulb, piriform, entorhinal and cingulate cortices, where it is localized in synaptic profiles.[228,229,656] Expression of PrP is maximal during synaptogenesis, a process accompanied by a shift of the protein from the developing axon to synaptic terminal fields.[657] Based on its subcellular distribution and on findings on altered structural reorganization in PrP-null

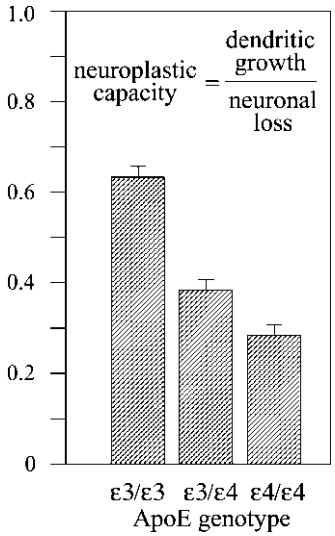

Fig. 4. The presence of the ApoE ε4-allele, a risk factor for AD, is associated with a decrease in the neuroplastic capacity (defined as the ratio of dendritic growth versus neuronal loss) of cortical pyramidal neurons. (Modified after Ref. 34.)

mice,[133] PrP has been suggested to be involved in stabilization of opposing synaptic membranes through adhesive mechanisms.[264,656]

2.1.7. Apolipoprotein E. Members of the low-density lipoprotein receptor (LDL-R) family and their ligands play a critical role in brain development and in neuronal remodelling in the adult nervous system (see Table 6). ApoE, a 34,000 mol. wt protein, is the major ligand of the LDL-R and the LDL receptor-related protein (LRP) in the brain.[93,318,467,741]

ApoE plays an important role in cholesterol and phospholipid transport, uptake and redistribution[599] and is also involved in the modulation of cell growth, cell-cycle control and differentiation.[111,185,340,474] Within the nervous system, apoE might be involved in maintaining synaptic integrity after injury and during ageing by several different mechanisms. Among them, recent studies have suggested that ApoE: (i) stabilizes the neuronal cytoskeleton; (ii) plays an important role in transporting esterified cholesterol to neurons undergoing reinnervation, where it is taken up by the LRP pathway and used as a precursor for the synthesis of new synaptic terminals; (iii) regulates interactions between neurons and the extracellular matrix (e.g. laminin); (iv) regulates levels of intracellular calcium;[500] and (v) controls cell-cycle progression.[788]

In mice deficient in ApoE, a loss of synaptophysin in nerve terminals and of MAP2-immunoreactive dendrites have been observed,[495] indicating that ApoE is necessary to preserve synaptic integrity. The ApoE4 allele frequency is markedly increased in both late-onset sporadic and familial AD.[139,600,660] Reduced levels of ApoE have repeatedly been reported in AD.[320,598] Isoform-specific differences in binding, internalization and degradation of ApoE[291] apparently associated with dysfunction of dendritic plasticity[34] might account for the ApoE4-associated risk of AD (Fig. 4).

2.2. Disturbances of morphoregulation—synapse loss and aberrant sprouts are the pathological hallmarks of Alzheimer's disease

Data obtained by electron microscopy, immunocytochemical and biochemical analyses on synaptic marker proteins in AD biopsies and autopsies indicate that synaptic loss is an early change and the major structural correlate of cognitive dysfunction (see Table 7).[63,95,161,169,259,662,267,296,314,434,483–485,487,489,490,499,501,505,757,795] Synaptic pathology is reflected by a loss of all major components of small synaptic vesicles and most peptides, stored in large dense core vesicles accompanied by extensive pathological changes of the synapse.[433] Although degeneration of subcortical input might contribute to cortical synapse loss,[13–15,20,21,29,35] most of the synaptic loss in the neocortex might derive from loss of cortico–cortical associational fibres,[330,446,501,503,542] i.e. from fibres arising in brain areas that normally retain a high structural potential in the adult brain.

AD is a slowly progressing disorder apparently preceded by a clinically silent period of several years or even decades. Similarly, synaptic degeneration is a slow process progressing from an initially reversible functionally responsive stage of down-regulation of synaptic function to stages irreversibly associated by marked synapse loss.[629] Recent findings of a deregulation of proteins involved in structural plasticity of axons and dendrites[309,372,461,520] as well as results of computational studies[308,329] indicate a failure of local neuronal regulatory mechanisms of synaptic plasticity and make a primary disturbance of synapse turnover very likely.

This assumption is further supported by alterations in the composition[59,275,476,744] and fluidity of membranes[211,678,840,841] as well as by direct morphological evidence of a disturbed axonal and dendritic remodelling (see Table 1).

As opposed to the continuous growth during ageing,[97,223] both axonal and dendritic proliferation in AD is restricted to certain cell types and stages of the disease[20,22,34] and is aberrant with respect to their localization, morphological appearance,[16,18,36,37,215] and composition of cytoskeletal elements.[470] Dystrophic neurites, mainly dendritic but occasionally also axonal in origin,[267,615] form a constant component of AD pathology. These neurites were originally regarded as aberrant sprouts by Fischer[220] (Fig. 5) and Simchowicz,[701] an assumption supported more recently by Golgi studies,[37,214,215,345,667] ultrastructural evidence[585] and the accumulation of growth-associated proteins, such as GAP-43, MARCKS, and spectrin, synaptic/axonal proteins and cytoskeletal proteins.[143,245,248,249,412,488,490,494,497,498,504,505,653] Aberrant sprouts can be detected rather early in AD,[345] apparently precede tangle formation and occur even without massive neuronal loss.[18,740] They might, thus, represent an event of primary significance, inherent to the pathomechanism rather than a response triggered by ongoing degeneration.[247,494,501]

Table 7. Synaptic alterations in Alzheimer's disease

Loss of molecular components of presynaptic plasma membranes
SNAP-25 Syntaxin 1/HPC-1 References: 130, 159, 174, 696
Loss of molecular components of synaptic vesicles
Synaptotagmin Synaptobrevin Synaptophysin Synapsin I rab3a p65 SV2 Clathrin assembly protein AP180 References: 68, 92, 94, 108, 159, 160, 296, 300, 313, 314, 327, 434, 455, 457, 489, 504, 505, 588, 658, 696, 748, 790, 795, 818, 829, 830
Loss of molecular components of postynaptic membranes
Neurogranin Drebrin E and A References: 116, 159, 301, 309
Morphological changes of synapses
Synaptic number in cortical regions is reduced by 30–50% while synaptic contact length is increased The **synapse-to-neuron ratio** is decreased by about 50% Density of neocortical synapses inversely **correlates with mental dysfunction** References: 2, 60–62, 168, 169, 533, 662–666, 719, 757
Brain imaging
Iodine-123 iomazenil (a specific tracer for the $GABA_A$ receptor, the dominant inhibitory synapse of the brain) as a measure of **loss of synapses** shows a reduced cortical distribution volume Reference: 717
EEG
Cordance and coherence, two quantitative EEG measures, allow non-invasive assessment of regional brain dysfunction associated with disturbances in **synaptic connectivity** in AD Reference: 138

2.3. Replay of developmental mechanisms as an endstage of a slowly progressing "morpho-dysregulation"

2.3.1. Re-expression of developmentally regulated genes. The aberrant neuritic growth in AD, as a likely indication of defect synapse turnover, is accompanied by microtubular reorganization[414,470] associated with the re-expression of a number of developmentally regulated proteins involved in morphoregulation, in particular cell-adhesion proteins such as PSA-NCAM[371,520] and cytoskeletal proteins such as the fetal form of alpha-tubulin and MAP5 (MAP1B)[17,23,24,87,250,262,305,382,538,808] (see Table 8).

MAP1B is the first MAP to be detected in the developing nervous system where its expression, particularly of its phosphorylated isoform (MAP1B-P), is associated with axonal growth.[273,469] Expression becomes down-regulated postnatally[507] and in the adult brain remains at relatively high levels only in regions that retain a capacity for structural plasticity.[568] There its distribution closely follows that of the embryonic PSA-NCAM rich in polysialic acid,[74] a developmentally regulated molecule involved in neurite growth and synaptogenesis,[151,553,680] suggesting that both molecules, overexpressed in AD, might play a role in structural remodelling of the adult brain.[568]

The notion of a replay of developmental mechanisms in the pathomechanism of AD is supported further by the occurrence of fetal-type post-translational modifications of cytoskeletal proteins that involve a particular developmentally regulated pattern of phosphorylation (see Table 8 and below).

Evidence indicating that the formation of abnormal growth profiles might be associated with an aberrant and elevated expression of growth factor receptors,[200,552] that precede neurofibrillary degeneration,[18] prompted us to suggest a sequence of events leading to neuronal degeneration and cell death in AD.[12]

This hypothesis proposes that it is the process of continous synaptic reorganization that becomes defective in AD. In this pathogenetic process, a subset of neurons retaining a high degree of plasticity and which are

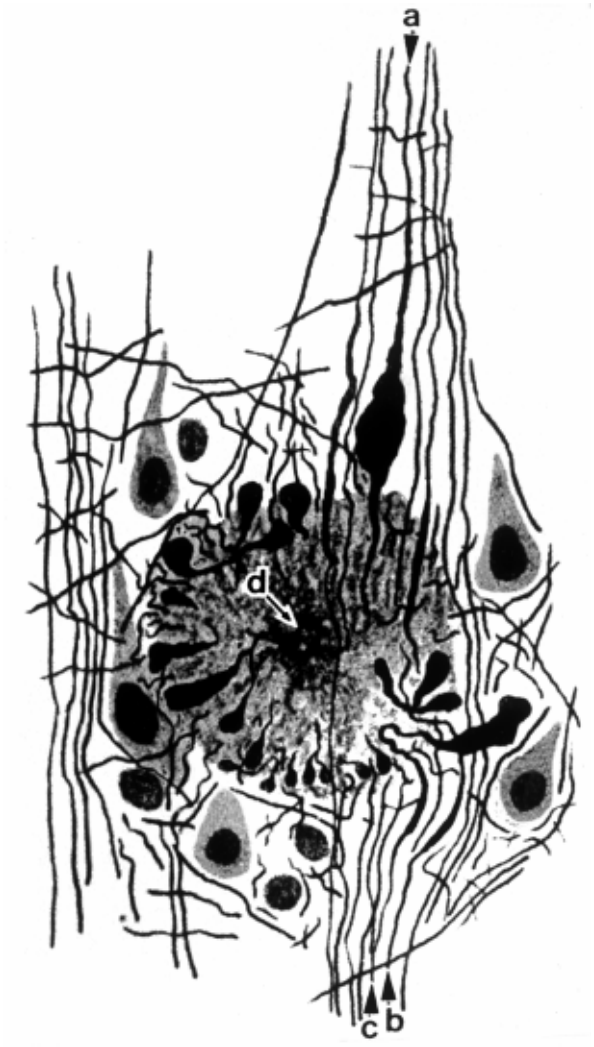

Fig. 5. In 1907 Oskar Fischer published a detailed description on the histopathology of senile dementia apparently not being aware of the somewhat earlier description by Alzheimer where he clearly regarded the thickened neurites seen in the periphery of plaques (Fig. 4 of Ref. 220; marked by c and b) as growing and aberrantly formed new neurites.

presumably in a "labile state of differentiation", are forced into a condition of dedifferentiation that is characterized by an expression of developmental regulated genes, post-translational modifications, and an accumulation of gene products to an extent that goes beyond those observed during regeneration. This replay of developmentally mechanisms might be the endstage of disturbed structural brain self-organization and a slowly progressing "morpho-dysregulation". This process of dedifferentiation involves molecular events that, in dividing cell populations, would lead to cellular transformation and is, thus, not compatible with the state of a neuron being irreversibly blocked from the re-entry into the cell cycle. It might, therefore, lead to neuronal death. From this hypothesis it can be predicted that those molecular events that are involved in neoplastic transformation might also play a key role in the pathomechanism of AD.[315] These mechanisms are notably a dysfunction of mitogenic signal transduction and cell-cycle control.

2.3.2. Mitogenic signal transduction in Alzheimer's disease. 2.3.2.1. Protein phosphorylation. The presence in the AD brain of growth-associated proteins, such as GAP-43, MARCKS, spectrin, heparan sulfate, laminin, NCAM, various cytokines and neurotrophic factors such as NGF,[137,153,200] bFGF,[265,388,732] EGF,[67,739] IL-1,[104] IL-2,[337] IL-6,[201] IGF-1,[136] IGF-2,[760] PDGF[444] and HGF/SF[210] as well as growth factor receptors[18] might be an indication of an increased trophic force particularly pronounced within the microenvironment of plaques (see also Table 1).

Mitogenic effects of these compounds are intracellularly mediated by a hierarchy of phosphorylation signals. These mechanisms of protein phosphorylation and dephosphorylation are normally involved in the regulation of neuronal plasticity[673,763] and, therefore, are essential to the basic processes of adaptive changes in the CNS. In AD, these phosphorylation processes are critically impaired[263,653] and might provide a link between disturbed mitogenic signalling, aberrant neuroplasticity, deregulation of cell-cycle control and cell death.

The cytoskeletal protein tau, the major component of PHF, may play a central role in the pathological cascade since tau can act as a link that transduces the trophic signal into cytoskeletal rearrangement, which might partly be responsible for the dendritic sprouting. Furthermore, tau in its hyperphosphorylated, aggregated form (PHF-tau) might disturb neuronal viability by interfering with axonal transport. However, a moderate elevation of the expression and phosphorylation state of tau has been associated with neuroprotection against apoptotic cell death.[25,26,202,444,524,558,819] Tau protein is more highly phosphorylated during mitosis.[610,613] Numerous phospho-epitopes incorporated into PHF are of a mitotic nature, displaying a temporally restricted pattern of appearance during M-phase in a variety of proliferating eukaryotic cells.[408,786] Those kinases that can phosphorylate tau in a PHF-like manner such as mitogen-activated protein (MAP) kinase,[183,261] glycogen synthase kinase 3β,[477] Cdc2/cyclin B1 kinase[439,785] and cdk5[64,584] are all associated with the cell cycle. Similarly, protein phosphatase 2A, able to dephosphorylate PHF-like tau and likely to be involved in abnormal phosphorylation processes in AD,[25,26,261,268] is cell-cycle regulated.[716]

2.3.2.2. The small G-protein p21ras. Proliferative and growth-stimulating effects of a number of growth factors that are elevated in early stages of AD are mediated by the activation of the MAPK pathway, which is also involved in modulating the expression and post-translational processing of APP and tau protein.[141,173,281,523,651] The activation of cell surface receptors of trophic and mitogenic factors is relayed to the downstream MAPK cascade by the small G-protein p21ras.

In mammalian cells, the p21ras gene product is encoded by a family of ras proto-oncogenes that include at least three functional loci, H-ras, K-ras and N-ras.[695] Binding of the neurotrophins to tyrosine kinase receptors (trk) converts p21ras from its inactive, GDP-bound, to active, GTP-bound, state. GTP-bound p21ras recruits

Table 8. Replay of developmental mechanisms in Alzheimer's disease

Re-expression of fetal proteins

Fetal Alz-50 clone 1 (FAC1), a DNA binding protein and transcriptional regulator
Embryonic alpha-tubulin
Embryonic beta-tubulin
hnRNP
Protein L-isoaspartyl methyltransferase (PIMT)
Ferritin heavy chain
Type IV collagen
Actin-binding protein cofilin
Profilin
C-series gangliosides
References: 83, 250, 370, 407, 538, 750, 808

Fetal-type phosphorylation of tau

Fetal tau shares many phosphoepitopes with PHF-tau, i.e. hyperphosphorylation of PHF-tau can be considered to consist of fetal-type phosphorylation and additional proline-directed and non-proline-directed phosphorylation
Tau on Ser 262, a phosphorylation site within the first microtubule-binding domain that is phosphorylated in fetal tau, adult tau and PHF-tau is phosphorylated by a **developmentally regulated 100,000 mol. wt protein kinase** exhibiting significantly greater activity in the embryonic rat brain than in the adult rat brain
PHF-1 immunoreactivity in the developing nervous system is associated with early stages of axon formation, both *in vivo* and *in vitro*, indicating an association between **axon growth and formation of the PHF-1 epitope**
References: 87, 90, 263, 306, 358, 382, 396, 442, 539, 609, 685

Re-expression and post-translational modifications of other fetal MAPs

Microtubule-associated protein MAP5 = **MAP1B** (the first MAP to be expressed in neurons and with an important role in neurite outgrowth) showing a fetal phosphorylation pattern is present in dystrophic neurites of senile plaques, neurofibrillary tangles and neuropil threads as well as neurons not yet affected by neurofibrillary degeneration
References: 247, 305, 366, 750, 776

Re-expression of neuronal thread protein

Neuronal thread proteins (NTP) are a family of phosphoproteins expressed in neuroectodermal tumour cell lines and in the brain during neuritic sprouting. The 15,000–21,000 mol. wt NTP cluster is associated with development and neuronal differentiation, whereas the 21,000 and 39,000–42,000 mol. wt species are **overexpressed** in AD, correlating with neurodegenerative **sprouting and synaptic disconnection**
References: 170, 814

Re-expression of cell-cycle-related proteins and formation of mitosis-specific epitopes

Expression of proliferation-associated proteins: p105, Ki-67, PCNA in variable subsets of neurons
Formation of **mitotic specific phosphoepitopes** in potentially vulnerable neurons prior to neurofibrillary degeneration
Association of PHFs with mitotic specific phosphoepitopes
Re-expression and deregulation of cyclin-dependent kinases: **cdk1, cdk4, cdk5**
Re-expression of **cyclins D, E, B, A** in variable subsets of neurons prior to neurofibrillary degeneration
Re-expression of **cyclin-dependent kinase inhibitors** $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$, $p19^{INK4d}$, $p21^{Cip1}$, $p27^{Kip1}$
References: 27, 28, 31, 33, 100, 408, 471, 493, 559–561, 709, 710, 785–787

raf-kinase from the cytoplasm to the plasma membrane, where it is activated.[730] Raf-kinase phosphorylates and activates the mitogen-activated protein kinase kinase (MAPKK) leading to the activation of the mitogen activated protein kinase (MAPK). During brain development, p21ras is involved in the regulation of the G_0/G_1 transition of the cell cycle and might, thus, be a critical regulator for cellular proliferation and differentiation.[75,76,156,212,747] In the adult nervous system, p21ras plays a role in reactive dendritic proliferation and neosynaptogenesis[595] that occurs in response to injury.

In early stages of AD, p21ras is already highly expressed in vulnerable brain areas prior to its affection by neurofibrillary degeneration, which makes a primary involvement in the pathomechanism very likely.[238] In more advanced stages of the disease, both neurons containing tangle-bearing material and neurons not affected by neurofibrillary degeneration as well as glial cells closely associated with plaques show a high expression[239] (see Fig. 6).

2.3.2.3. Nitric oxide and the process of self-perpetuation of neurodegeneration. p21ras is also activated by nitric oxide (NO) and intermediates generated through oxidative stress.[826] Thus, NO might be a key mediator linking cellular activity to gene expression and long-lasting neuronal responses through activating p21ras by redox-sensitive modulation.[164] In AD, nNOS, the neuron-specific NO synthesizing enzyme is aberrantly expressed in potentially vulnerable neurons of the isocortex and entorhinal cortex. Since these neurons express nNOS prior to their affection by neurofibrillary degeneration,[463,465] transcriptional induction of nNOS might be an early event in the process of neurodegeneration.

nNOS was originally thought to be a constitutively expressed enzyme. It becomes increasingly clear now, however, that its levels are dynamically regulated in response to neuronal development, plasticity and injury.[164,165,225] The transcriptional induction of nNOS that is controlled by neurotrophins and other growth factors,[322,592,605] is in turn involved in regulating the expression of immediate-early genes in neurons,[540] thereby controlling neuronal growth and differentiation[319,591,592] and might thus be part of the neuronal reparative/regenerative response to injury.

NO may play a major role in nervous system morphogenesis and plasticity and may be involved in activity-dependent establishment of connections in both developing and regenerating neurons.[164,464,648,714,812,817,825] Under developmental conditions, NO may trigger growth arrest, a process that at least in certain cell types, might involve inhibition of cdk2, a key regulator of the G_1 and S phases of the cell cycle (see below). These antiproliferative effects of NO involve the repression of cyclin A re-expression as well as an induction of the cyclin-dependent kinase inhibitor $p21^{Cip1}$.[242,349,605] The high degree of co-expression of nNOS with $p16^{INK4a}$,[465] indicates that further regulators of the G_1–S-transition might be involved in the NO-induced cell-cycle arrest or that additional mechanisms of proliferation and differentiation regulating mechanisms are activated in parallel in the course of neurodegeneration in AD. Thus NO serves as an inducer of cell-cycle arrest, initiating the switch to cytostasis during differentiation,[164,422,592] a process that can alternatively lead to apoptosis.[242]

Although the molecular mechanism for the control of NO in proliferation, differentiation, cellular survival and death is not understood in detail, recent evidence indicates that activation of p21ras, a potential endogenous NO-redox-sensitive effector molecule, is critically involved.[428,430,826] p21ras is essential for NO downstream signalling and endogenous NO can activate p21ras in the same cell.[429] Activation of the p21ras-dependent MAP-kinase cascade by NO may be mediated by direct activation of ras-GTPase activity.[428,429,546] NO-dependent activation of p21ras may also mediate activity-dependent survival of immature cortical neurons.[269]

As expression of nNOS in AD is highly co-localized with p21ras,[465] an autocrine loop may exist within cells, whereby NO activates p21ras that in turn leads to cellular activation and stimulation of NOS expression.[430] The co-expression of NOS and p21ras in neurons vulnerable to neurofibrillary degeneration early in the course of AD clearly provides the basis for a feedback mechanism that might exacerbate the progression of neurodegeneration in a self-propagating manner (see Fig. 6). This self-perpetuation of a process likely to be associated with limited prospects of physiological control and termination might be the critical switch converting two potentially neuroprotective mechanisms such as NO[208,269] and p21ras[321] dependent signalling into a disease process leading to slowly but continuously progressing neuronal death.

2.3.2.4. Mitogen-activated protein-kinase cascade. The MAPKs or extracellular signal regulated kinases (ERKs) and MAPKK or MAP/ERK kinase (MEK) belong to a group of protein kinases which is highly conserved from yeast to vertebrates.[81] They are key molecules in signal processing that become activated in response to a wide variety of reagents. Among these are tumour promotors, interleukins, growth factors whose receptors are tyrosine kinases, mitogens whose receptors couple to heterotrimeric guanine nucleotide binding proteins (G proteins), and agents that induce *N*-methyl-D-aspartate receptor activation.[80,587] When activated, ERKs rapidly phosphorylate targets that lead to changes in kinase cascades, protein function or gene expression. Effectors include Ser/Thr kinases ($pp90^{rsk}$, MAPK-activated protein kinase-2 and 3p-kinase), transcription factors (Elk-1, c-Myc, c-Jun, NF-116 and ATF-2) and structural proteins (talin, microtubule-associated proteins and lamins).[122,123,218,453,617,681,686]

The MAP kinase, referred to as p42 or ERK2[183,261] and perhaps other members of the MAPK family are able to phosphorylate recombinant tau *in vitro* and convert it to a form which is similar to PHF tau.

In AD, the expression of both MAPKK and MAPK is increased.[30] Elevation of both kinases is most pronounced during early stages of the disease and is inversely related to the tissue content of abnormally phosphorylated PHF-tau.[30] Pronounced immunoreactivity of MAPKK and MAPK is present in potentially vulnerable neurons still unaffected by neurofibrillary degeneration as well as in tangle-bearing neurons that are likely to be metabolically highly compromised. The subcellular translocation of MAPK from the cytoplasmic to the nuclear compartment provides additional evidence for an activation of this signal pathway in the pathomechanism of AD[30,481] (see Fig. 6).

A protein that has recently been suggested to participate in cell transformation and mitogenic signalling pathways is the 14-3-3 protein.[541] The 14-3-3 protein interacts with the Raf-kinase, a component of the MAPK cascade, as well as with other proto-oncogenes

Fig. 6. Schematic illustration of the intracellular signalling events triggered by morpho-dysregulation in AD that involve an aberrant activation of p21ras/MAP-kinase signalling, a loss of differentiation control, the subsequent re-entry and partial completion of the cell cycle and eventually result in cell death. The immunohistochemical localization of major molecular components involved in these processes is shown in insets. Upper left panels: Elements of the p21ras/MAP-kinase cascade. p21ras is highly expressed in potentially vulnerable neurons prior to PHF formation, in tangle-bearing neurons and plaques. The high expression of B-Raf and p 14-3-3 is associated with PHF formation. MAPKK (MEK) and MAPK (ERK1/2), localized to the cytoplasm and not found in nuclei in control brain, are subcellularly translocated to nuclei in AD (arrows) indicating an activation of these kinases prior to PHF formation. Upper right panel: Aberrant expression of nNOS. nNOS is ectopically expressed in potentially vulnerable pyramidal neurons prior to PHF formation. Lower panels: Regulators of the activation and orderly progression through the cell cycle. Cell cycle associated proteins are highly expressed in potentially vulnerable neurons in AD prior to PHF formation. In more advanced stages of the disease, they are associated with PHFs. Scale bars = 20 μm.

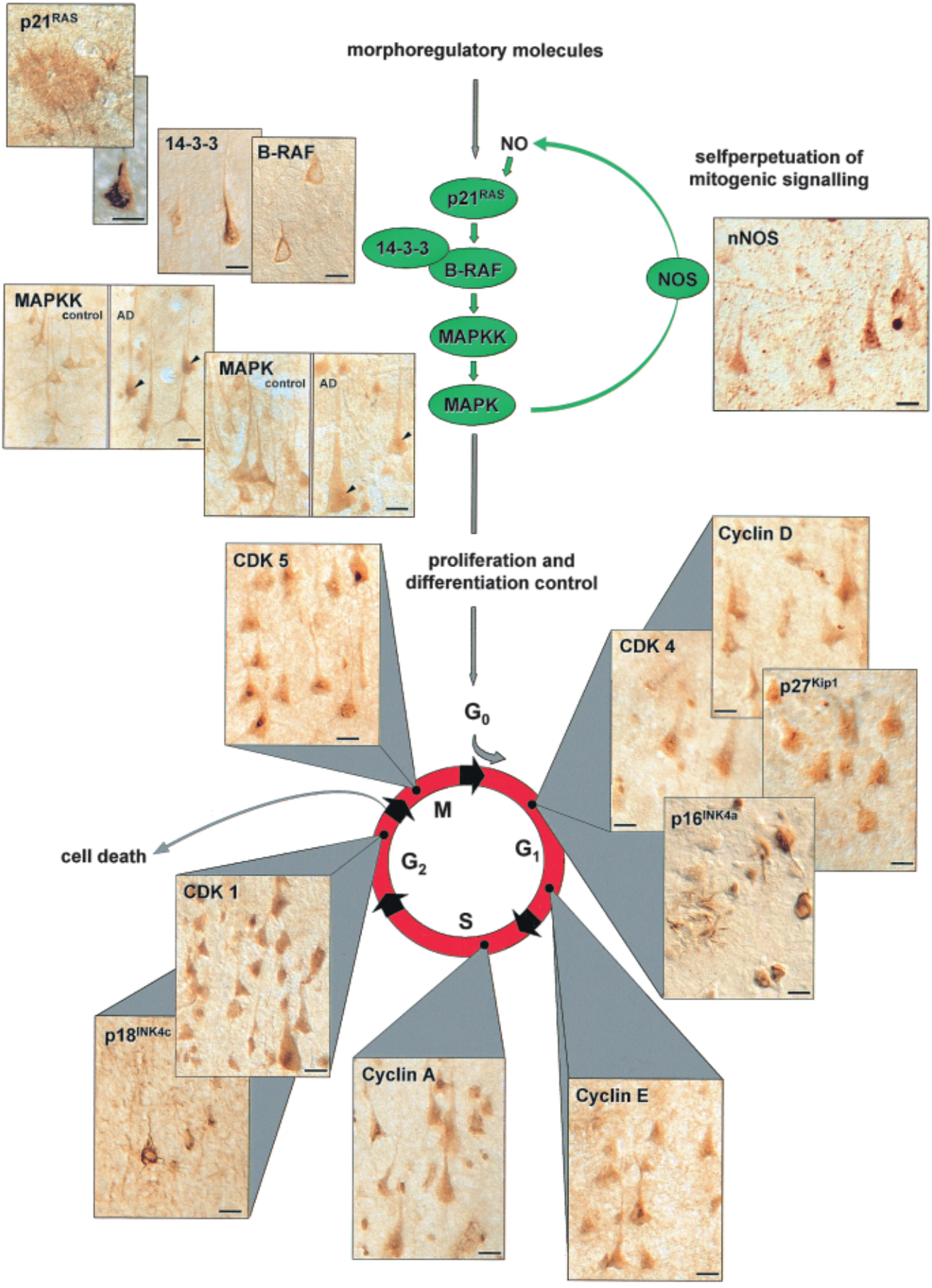
p21RAS
morphoregulatory molecules
NO
selfperpetuation of mitogenic signalling
14-3-3
B-RAF
p21RAS
14-3-3
B-RAF
MAPKK
MAPK
NOS
nNOS
MAPKK control
AD
MAPK control
AD
CDK 5
proliferation and differentiation control
Cyclin D
CDK 4
p27Kip1
G0
M
G1
G2
S
p16INK4a
cell death
CDK 1
p18INK4c
Cyclin A
Cyclin E

Fig. 6.

and oncogene products, thereby modulating these signalling proteins. The 14-3-3 proteins represent a highly conserved family of dimeric proteins that are widely distributed among eukaryotic cells. At least seven isoforms have been identified in mammalian tissue. They are remarkably abundant in the brain where they constitute about 1% of the cytosolic protein. In AD, expression of 14-3-3 protein is increased, closely associated with neurofibrillary tangles and dystrophic neurites within neuritic plaques[237] (see Fig. 6).

2.3.3. Loss of cell-cycle control and dedifferentiation in Alzheimer's disease. The data presented above suggest that the activation of the p21ras/MAPK cascade that plays an essential role in transmitting proliferative responses is also involved in early steps of the pathomechanism of AD. The induction of cell proliferation by MAP kinase has been shown to be a direct result of increased transcription of many immediate-early genes[121,684] including cyclin D1. In transforming cells, moreover, p21ras is involved in the regulation of the G_0/G_1 transition of the cell cycle mediated through cooperation with cyclin D1.

Expression of cyclin D1, a critical regulator of the transition from the G_0 to the G_1 phase of the cell cycle [1,436] that acts through activation of cdk4, is increased in neurons prone to neurodegeneration in AD.[31,100] Cyclins other than D1 such as cyclins E and A involved in regulation of G_1–S-transition as well as cyclin B regulating G_2–M-transition[31,559,709,785] are also elevated (see Fig. 6).

Several cyclin-dependent kinases critical for the progression through the cell cycle[403] such as cdk1 (cdc2), cdk4 and cdk5 are deregulated in AD.[64,100,439,561,584,785] The cdk1 (cdc2) kinase is able to phosphorylate tau protein at sites known to be phosphorylated in AD[401,439] (also see Section 2.3.2.1). APP, furthermore, is phosphorylated both *in vitro* and in intact cells by a cdk1 (cdc2)-like kinase in a cell cycle-dependent manner which is associated with altered production of potentially amyloidogenic fragments containing the entire β/A4-domain.[743]

Activation of cyclin-dependent kinases is negatively regulated by proteins of the cyclin-dependent kinase inhibitor (cdki) family which bind directly to cdk4/6 or to complexes of cdk4/6 with D-type cyclins.[66,71,140,290,299,324,682,690] Cyclin-dependent kinase inhibitors can be classified into two groups based on the structure of the protein. One group, the INK4 family, includes $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$ and $p19^{INK4d}$ which have an ankyrin repeat motif. The $p21^{Cip1}$ and $p27^{Kip1}$, which contain a homologous amino-terminal cyclin-dependent kinase inhibitory domain, belong to the other group.[66,71,698] The INK4 family of cyclin-dependent kinase inhibitors might be involved in the regulation of pathways that control cell growth and proliferation as well as cell death. Deregulation of these cdki-proteins results in either uncontrolled proliferation and neoplastic transformation or activation of apoptosis. Recent studies demonstrate that activation of endogenous cyclin D1-dependent kinases is essential during neuronal apoptosis.[231,416,456]

A prominent representative of the INK4 family is $p16^{INK4a}$.[682] Recent evidence implicates the $p16^{INK4a}$ protein in pathways for control of cell growth and proliferation and demonstrates that $p16^{INK4a}$ can function as a tumour suppressor protein to G_1-arrest cells.[106,381] $p16^{INK4a}$ apparently inhibits cdk4 by binding in competition with cyclin D.[682] Malignant cellular transformation has been shown to produce major changes in the modulation of the cyclin-cdk complexes by associated cdki-proteins such as $p16^{INK4a}$. A recent study[416] clearly shows that the overexpression of the cyclin-dependent kinase inhibitor $p16^{INK4a}$ protects neurons from apoptotic cell death.

In AD, we observed an increased expression of $p16^{INK4a}$ and other members of the INK4 family of the cyclin-dependent kinase inhibitors interacting with cdk4/6 such as $p15^{INK4b}$, $p18^{INK4c}$ and $p19^{INK4d}$ that was closely related to neurofibrillary tangles and neuritic components of plaques, while alterations of $p21^{Cip1}$ and $p27^{Kip1}$ were less constant.[27,28,33]

The induction of the proto-oncogene p21ras[239] and cyclin-dependent kinase inhibitors of the INK4 family[27] in AD is paralleled by experimental *in vitro* studies on primary human or rodent cells showing that expression of p21ras induces $p16^{INK4a}$ and subsequently results in a permanent G1 arrest. This G1 arrest induced by p21ras and accompanied by accumulation of $p16^{INK4a}$ is phenotypically identical to premature cellular senescence.[683] Expression of dominant-inhibitory p21ras, furthermore, can rescue neuronally differentiated PC12 cells from death caused by NGF withdrawal, implying a relationship between proliferative capacity and cell death.[212] We have shown previously that a high capacity of structural neuronal plasticity in the adult brain might predispose neurons to tangle formation in AD.[20,22] This high potential of neuroplasticity associated with the necessity of synaptic turnover and reorganization might require properties inherent to both growth cones and synaptic connections.[593] These neurons might, thus, retain "immature" features and might not be "fully differentiated", i.e. arrested in G_0, an assumption supported by recent finding on the expression of cyclin B and E in hippocampal neurons of healthy elderly subjects.[559,709]

It is, therefore, suggested that the re-expression of developmentally regulated genes, the induction of post-translational modifications and accumulation of gene products to an extent which goes beyond that observed during regeneration and the aborted attempt of "differentiated" neurons to activate the cell cycle, which apparently is a critical event in the pathomechanism of AD,[12,27,28,31,34,100,357,471,492,559–561,709,710,785–787] is due to a loss of differentiation control that normally is involved in the regulation of neuronal plasticity.

It might, thus, be a "labile fixation" of plastic neurons in G_0 which allows for ongoing morphoregulatory processes after development is completed. The delicate balance, however, between G_0 arrest and G_1 entry might be prone to a variety of potential disturbances during the lifetime of an individual. Morphodysregulation in AD, accompanied by aberrancies in intracellular mitogenic signalling might, thus, be a slowly progressing dysfunction that eventually overrides this differentiation control and results in de-differentiation, a condition in

conflict with the otherwise "mature" background of the nervous system. Cell-cycle and differentiation control might thus provide the link between structural brain self-organization and neurodegeneration,[12,315] both of which in the human brain have reached a phylogenetic level unique in nature.

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