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Perspective

Could ecosystem management provide a new framework for Alzheimer's disease?

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Abstract Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder that involves a plethora of molecular pathways. In the context of therapeutic treatment and biomarker profiling, the amyloid-beta (Aβ) peptide constitutes an interesting research avenue that involves interactions within a complex mixture of Aβ alloforms and other disease-modifying factors. Here, we explore the potential of an ecosystem paradigm as a novel way to consider AD and Aβ dynamics in particular. We discuss the example that the complexity of the Aβ network not only exhibits interesting parallels with the functioning of complex systems such as ecosystems but that this analogy can also provide novel insights into the neurobiological phenomena in AD and serve as a communication tool. We propose that combining network medicine with general ecosystem management principles could be a new and holistic approach to understand AD pathology and design novel therapies.

Keywords: Alzheimer's disease; Amyloid-beta peptide; AD therapy; Ecosystem management; Eutrophication; Spatiotemporal dynamics; Aβ alloform; Network medicine; Communication

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, affects the human brain and causes severe memory loss and behavioral changes. Despite some promising drug candidates targeting AD, clinical trials, however, remain unsuccessful due to a lack of efficacy or safety issues [1]. Current treatment is still limited to the alleviation of disease symptoms without the arrest or reversion of the underlying disorder. This lack of success reflects the general failure to fully comprehend the neurobiology of AD and the underlying pathogenesis. As multiple biochemical pathways are affected in AD, it is conceivable that targeting only one disease pathway might have an overall negligible effect as other disease mechanisms and pathways could still play a dominant role.

The main molecular hallmarks of the disease are the formation of amyloid plaques and neurofibrillary tangles

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(NFTs), which ultimately result in neuronal dysfunction and neuronal cell death [2]. In addition to the deposition of the amyloid-beta (Aβ) peptide and the hyperphosphorylation of tau, AD pathology also includes neuronal degeneration, an impaired microvasculature, a dysfunctional blood brain barrier, neuroinflammation, mitochondrial deterioration, oxidative stress, cytoskeleton disintegration, and epigenetic changes [3]. Although the amyloid cascade hypothesis is still influential to explain the pathophysiology of AD, alternative views consider tau as the main driving force of AD [4] or deem that several pathogenic features of AD can be interpreted as amyloid-independent alterations of synaptic plasticity, endolysosomal trafficking, cell cycle regulation, and neuronal survival [5]. Another hypothesis suggests that AD results from accelerated neural and cognitive decline in the vulnerable, aged brain due to microvascular failure and decreased angiogenesis [6]. In most cases, AD thus results from the interplay between certain susceptibility genes, environmental factors, and lifestyle contributors [7]. Therefore, it is essential that drug development strategies not only address the complexity of a single disease component (e.g. Aβ, tau, neuroinflammation…) but also address the multifactorial nature of this disease and the dynamics of the various interacting disease-contributing factors [8]. Developing new therapeutic strategies is indispensable as AD incidence is predicted to nearly triple by 2050 if no cure becomes available [9].

In an effort to approach AD from a different angle, we postulate that a similar complexity can be observed in complex systems such as ecosystems, which can be defined as networks of interactions among species and their environment [10]. In ecosystems, the relative abundance of the composing species is continuously molded by environmental conditions affecting the relative population growth of species, priority effects (i.e. order of emergence or arrival of species [11]), and biotic interactions among species [12]. As a result, community structure may change over time, and the resulting trajectories may lead to different equilibria or oscillations [13] that, in turn, will determine the functions and services provided by the system (e.g. productivity, efficiency of biochemical cycles, and resistance against invasive species). Similarly, the temporal dynamics in the composition of disease factors may also be governed by inter- and intra-molecular interactions, changes in environmental conditions, and priority effects [14]. The end point of the evolution of a complex system may be deterministic (e.g. the formation of plaques in AD, the eutrophication of a lake, ecological succession toward a climax forest after a fire…), but the route to get there may not be. For instance, some elderly people retain a normal cognitive function despite having a high amyloid load in their brain, whereas others show severe cognitive decline with little Aβ deposition [15]. There could also be different end points, some of which may be preferable over others (e.g. turbid vs. clear water states in lakes, tree savannah vs. grass savannah). Finally, the stochastic nature of community trajectories should be investigated as order of arrival (priority effects) or small initial deviations followed by positive feedbacks could reduce the predictability of responses [13]. Based on these insights from ecosystem ecology, we postulate that a better knowledge of the interplay between the drivers that determine variation in the temporal trajectories of disease-contributing factors, by minimizing or avoiding trajectories that are associated with toxicity and neurodegeneration, may render AD treatment more effective.

This perspective article explores the parallel that exists between the complexity of the molecular interactions within AD and the complex architecture of direct and indirect interactions in ecosystems (Fig. 1). We propose that insights from ecology, community assembly theory, and ecosystem management principles, in particular, (Box 1) might provide novel useful insights into AD pathogenesis and could serve as a guiding principle for innovative therapy design. Moreover, this framework provides an additional opportunity to establish a dialog between researchers, medical experts, industrial partners, and the lay public (patients and caregivers) using more familiar observable natural events as proxies for molecular and cellular events in AD. The power of such a communication strategy is nicely illustrated with the cover image of the November 2014 issue of this *Journal*, which depicts the North American woodpecker. As described in the editorial, the "woodpecker model" provides a comparative mind-set to gain more insight into the link between traumatic brain injuries and the subsequent development of neurodegenerative diseases [17].

2. Comparison of Aβ behavior in AD with general ecosystem principles

As the idea originated from the viewpoint of bench scientists investigating the role of Aβ in AD, we have used the Aβ peptide as an example to showcase some of the commonalities between AD complexity and ecological principles. The main driving force for writing this perspective is the emerging picture of increasing complexity for Aβ aggregation, whereby Aβ dynamics at different levels play a crucial role in AD [14]. Yet, that picture remains incomplete as all therapeutic intervention strategies that target Aβ production, accumulation, or clearance have failed hitherto and there is still no means to cure or even halt the disease [3]. This fact alone provides strong support for the development of a combination therapy to tackle AD. Thus, this ecosystem paradigm should not be limited to Aβ as a disease-contributing factor, but similar analogies can be envisioned with other disease components (e.g. tau, neuroinflammation…) that can be combined in more complex models.

Ecosystems can be perceived at different levels in the context of AD: the brain, the extracellular space, or

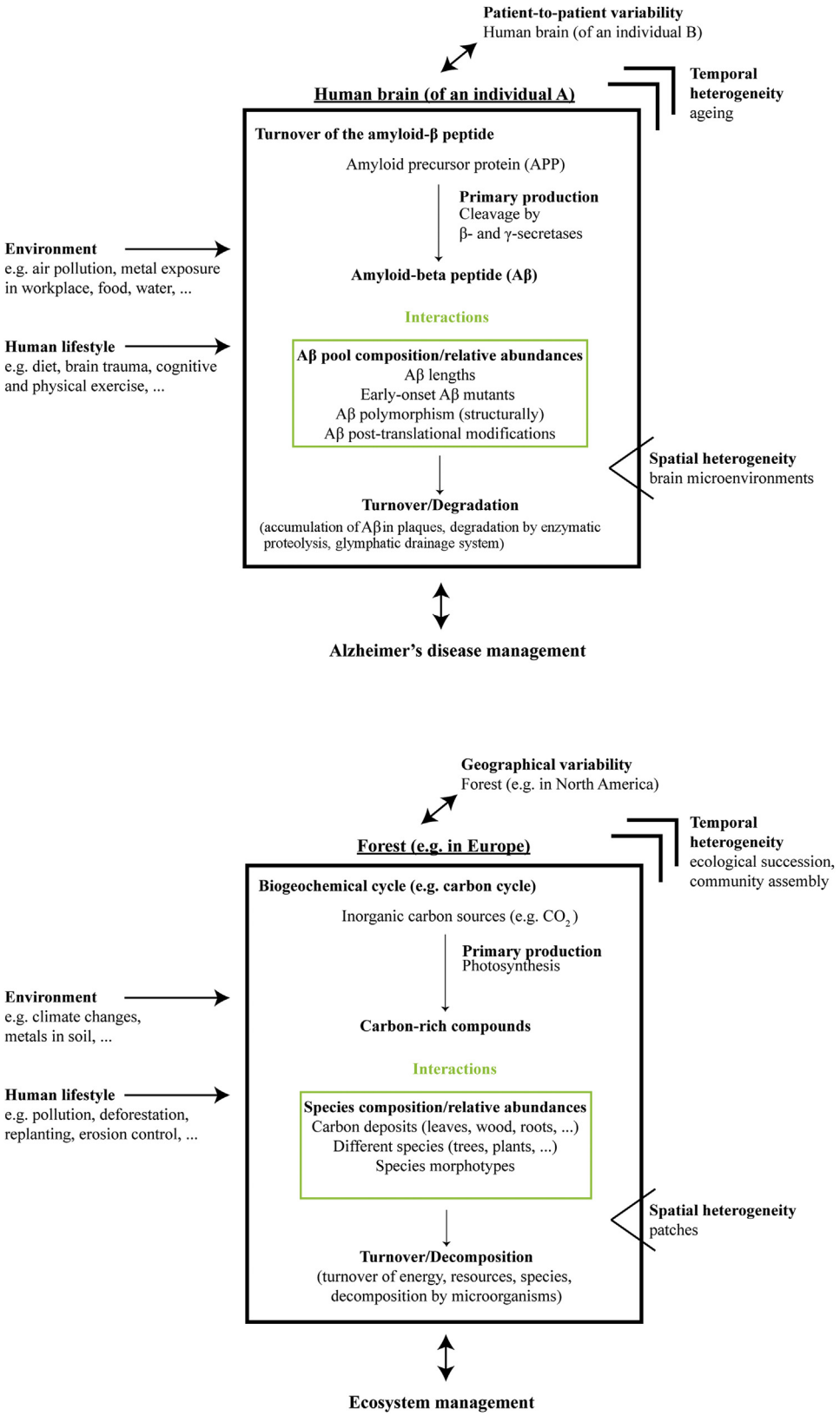

Fig. 1. A schematic comparison of the Aβ-flux in the context of Alzheimer's disease and the carbon-flux in an example of an ecosystem. The Aβ peptide is considered as a central player in AD and can be depicted in a network of many interacting molecules. Influences of the environment and an individual's lifestyle can contribute to disease outcome. The commonalities between the Aβ network and the complexity of an ecosystem reveal a conceptual framework that can lead to the development of more efficient AD therapeutic strategies. This illustration is an oversimplification to highlight the ecosystem paradigm and does not reflect the physiological roles of APP, Aβ, and the secretases. Abbreviations: Aβ, amyloid-beta; AD, Alzheimer's disease.

Box 1
Use of the term "Ecosystem management"

We define ecosystem management as the management of abiotic factors and/or biotic interactions in a natural environment of interacting species to maximize ecosystem services. Ecosystem services are the direct and indirect contributions of ecosystems to human well-being [16]. When natural resource management is applied to the whole ecosystem, rather than a single species, it is termed ecosystem management (Fig. 2A). Key aspects of ecosystem management include

- Integration of ecological, social, and economic goals and recognition of humans as key components of the ecosystem.
- Accounting for the complexity of natural processes and social systems and using an adaptive management approach in the face of resulting uncertainties by carefully monitoring various parameters.
- Incorporating understanding of ecosystem processes and how ecosystems respond to environmental perturbations.
- Emphasizing the protection and restoration of ecosystem structure, function, and key processes.

The fundamental objective of ecosystem management is long-term stability. In this context, manipulative experiments that aim to push an ecosystem into another state and sound ecological models that incorporate multiple stable states and alternative trajectories to capture the complex dynamics of ecosystems play an important role to achieve this goal [10].

Box 2
Use of the term "Aβ alloform"

An Aβ alloform is defined as a distinct form of the Aβ peptide that is commonly treated as a single kind of peptide species. This includes the different Aβ peptide length variants and posttranslational side-chain modifications. Aβ peptides are generated from the transmembrane amyloid precursor protein (APP) by sequential cleavages by β-secretase and γ-secretase. The β-secretase cleavage site is fixed, but imprecise γ-secretase cleavage at the C-terminal end results in Aβ peptides of various lengths ranging from 37 to 49 amino acids. The most abundant forms are $A\beta_{1-40}$, composed of 40 amino acids, and $A\beta_{1-42}$, that is C-terminally extended by two hydrophobic residues, making this alloform more aggregation prone. Furthermore, Aβ peptides can undergo posttranslational side-chain modifications including racemization, isomerization, phosphorylation, oxidation, nonenzymatic glycation and pyroglutamylation [14]. Mass spectrometry (in combination with immunoprecipitation) is the most frequently used method to gain insight into the composition of the Aβ peptide pool in the brain or CSF. Aβ alloform mixtures behave in a more complex manner than when studied in isolation in terms of aggregation behavior, dynamics, and toxic properties [23–25]. However, the complexity of the "Aβ system" is still a largely unexplored field of study, hampering a good understanding of the neurobiology of AD. Therefore, interactions between Aβ alloforms require further investigation and should be considered when designing new therapeutic strategies.

specific subcellular compartments (e.g. mitochondria). Similarly, in nature, one could consider e.g. a forest, an individual tree, or even a leaf as ecosystem boundaries. The choice of ecosystem boundaries will define the subset of "species" and interactions to include in the analysis, although the boundaries are not necessarily absolute. In this example, the human brain can be considered as an ecosystem (Fig. 1).

There is a flow of Aβ throughout the life span of an individual. The production of Aβ is a physiological process that occurs in neuronal cells and is essential for normal synaptic activity [18]. There is a tight regulation of Aβ production with its degradation that occurs via receptor-mediated transfer across the blood brain barrier, enzymatic proteolysis (e.g. insulin-degrading enzyme, neprilysin) [19], or the glymphatic drainage system [20]. Similarly, biogeochemical cycles that move chemical substances (e.g. water, carbon-rich compounds, and so forth) through the biotic and abiotic compartments of an ecosystem are critical for life. These molecules may be recycled or accumulated in a sink/reservoir, such as different ecosystem compartments species, tissues, or biomass [10]. Similarly to an imbalance between Aβ production and clearance that can result in Aβ accumulation in plaques throughout the brain [21], aberrations in biogeochemical cycles can alter the structure and functioning of natural and managed ecosystems [22].

The Aβ monomeric peptide pool in the brain contains multiple different Aβ variants, including different peptide lengths and side-chain modifications. We will collectively refer to all these Aβ variants as Aβ alloforms (Box 2). In addition to Aβ species' diversity described previously, several Aβ mutants have been linked to the familial type of AD that occurs at early age, defined as before the age of 65 [26]. Taking Aβ peptide pool diversity into account, a parallel can be seen with variation in the relative abundance of species' ecological communities or in the relative abundance of genotypes in populations. In both cases, interactions occur between entities, that differ in the effects they have on overall ecosystem functioning.

The in vivo Aβ peptide pool is a complex mixture of Aβ species influencing one another, similar to the interactions that occur between species in an ecosystem [10]. It has now been recognized that the composition of this

pool, rather than the absolute Aβ quantity, plays a prominent role in disease outcome as different Aβ alloforms can influence each other's aggregation behavior and toxic properties [23–25]. For example, shifts in the $A\beta_{1-42}$:$A\beta_{1-40}$ ratio can modulate the formation of neurotoxic oligomers [23]. Minor traces of $A\beta_{1-38}$ can render $A\beta_{1-40}$ toxic to a neuroblastoma cell line while exerting a cytoprotective effect on $A\beta_{1-42}$ [25]. Moreover, the interplay between different Aβ aggregation states must also be considered, as they exist in a dynamical equilibrium, and it has been suggested that the ongoing aggregation, rather than a specific toxic entity, is responsible for Aβ-related toxicity [27]. The inherent dynamical character of the Aβ system [14] is in agreement with the fact that ecosystems are dynamical entities [10].

Mounting evidence shows that environmental factors influence AD and Aβ properties. Air pollution has been reported to accelerate Aβ accumulation and induce oxidative stress [28]. Metals (Cu, Zn, Fe, and Al) colocalize with Aβ plaques and induce Aβ toxicity through enhanced Aβ aggregation and production of reactive oxygen species [29]. Stress or exposure to environmental toxins can also induce epigenetic changes related to memory and learning. In this regard, exposure to lead early in life has been demonstrated to upregulate genes involved in AD late in life in primates, through mechanisms involving DNA methylation and histone acetylation [30]. Recent postmortem brain tissue analysis have yielded the first evidence that the lifestyle changes that increase AD risk may be taking effect through epigenetic changes of gene function [31,32]. However, more research is required to reveal if those epigenetic changes play a causal role in AD or occur as a result of it. Interestingly, as epigenetic changes are potentially reversible, they may provide targets for the development of new therapies as suggested for AD associated with Down syndrome [33]. Exposure to synthetic pesticides is also associated with increased risk of late-onset AD [34], although these compounds have profound effects in natural ecosystems [35]. Similarly, environmental stressors can change the temporal trajectories of ecosystems resulting in unfavorable ecosystem states such as turbid ponds (Fig. 2), bleached coral reefs, or nutrient-depleted soils [37]. In addition, in response to environmental stimuli, epigenetic changes may occur that can affect important ecological phenomena (e.g. response to invasive species, disease susceptibility…). Moreover, epigenetics may contribute to the process of adaptation [38]. Adaptability and inertia (i.e. resistance to adapt) can help an ecosystem to respond to environmental change to a certain extent. Additionally, numeric advantages e.g. via priority effects can inhibit or slow down ecosystem responses to environmental change.

Human lifestyle has been suggested to be associated with AD development and Aβ properties. Several food components have been proposed to be potent inhibitors of Aβ aggregation or to act as anti-inflammatory molecules or antioxidants [39]. Prolonged cognitive and physical exercise has been shown to have a positive effect on the rate of cognitive decline [40]. In contrast, severe brain injury [41] and type II diabetes [42] are important risk factors for AD development. Similarly, environmental change (including human impact) is a main driver of ecosystem trajectories [10]. The behavior of humans can affect ecosystems in numerous ways, e.g. by pollution, deforestation, and over-fishing but also by replanting and sustainable energy usage. Certain discrepancies should, however, be noted. In the case of AD, lifestyle affects the state of the individual itself, whereas in the case of an ecosystem, humans impact the entire system around them, which ultimately may impact the state of the individual (e.g. air pollution may cause asthma).

Temporal changes in the brain associated with aging are the most important risk factors for AD development (temporal heterogeneity). Aging is associated with defective protein synthesis, with less efficient quality control mechanisms, and with cumulative oxidative damage. However, the contribution of aging to AD is highly complex and still not yet fully understood [43]. Likewise, ecosystems are often not stable over time and may evolve from one equilibrium to another or experience regular cycles. This process is driven by birth and death rates (demography), colonization dynamics, extinction, and priority effects. The latter implies that the presence of some species may inhibit or facilitate the settlement of others, resulting in ecological succession [13]. These phenomena can compare in AD to the synthesis and clearance rates of Aβ, the distribution pattern of Aβ in the brain (*cfr* next paragraph), and to the effects of particularly damaging variants of molecules in specific brain compartments (e.g. an increased $A\beta_{1-42}$:$A\beta_{1-40}$ ratio, occurrence of oxidized Aβ …).

Furthermore, the major neuropathologic hallmarks of AD such as amyloid plaques and NFTs display a distinctive spatiotemporal distribution in the brain. The neurofibrillary degeneration starts in the allocortex of the medial temporal lobe, spreading to the associative isocortex and finally affecting all isocortical areas, with the associative areas being affected before and more severely than the primary sensory, motor, and visual areas. In contrast to NFTs, amyloid plaques accumulate mainly in the isocortex, with the allocortex being affected to a lesser extent and later than the associative isocortex. Among the isocortical areas, as for NFTs, primary sensory, motor, and visual areas tend to be less involved compared with association multimodal areas [44]. This distinct temporal and regional distribution of the neuropathologic hallmarks suggests a regional susceptibility or vulnerability to the ongoing pathophysiological processes. La Joie et al. (2012) evaluated concomitantly Aβ deposition, hypometabolism, and gray matter atrophy in a brain region-specific manner in AD patients. They demonstrated marked regional variability in the hierarchy between these different brain alterations and speculated that these reflect the differential involvement of region-specific pathologic or protective mechanisms, such as the presence of NFTs, disconnection, and compensation

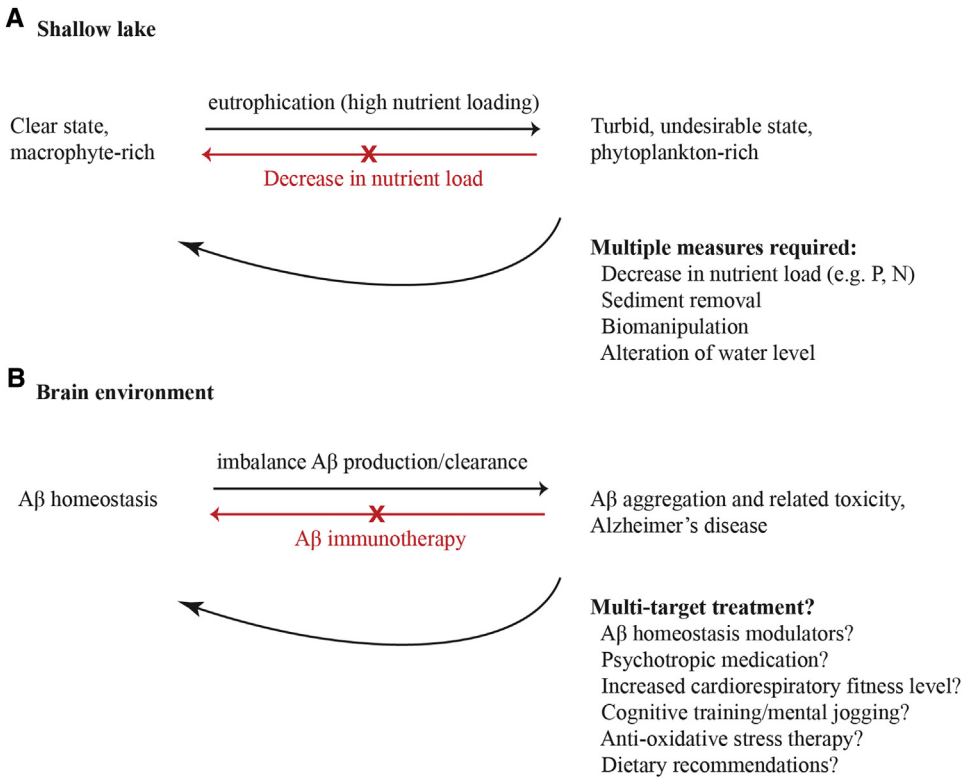

Fig. 2. Ecosystem management principles may be useful to develop more effective AD therapies. (A) Shallow lakes can typically occur in one, two, or more different equilibrium states: a clear state with submerged macrophytes or a turbid state dominated by phytoplankton. Both states are characterized by major biotic differences, some of which stabilize the system in the respective state, with resilience to impacts. If the limiting nutrient (e.g. P, N) load of the lake exceeds a critical value, eutrophication may cause a switch from the clear state to the turbid state that is generally considered as undesirable because plant communities and rich fish fauna disappear and biodiversity decreases. In many cases, nutrient reduction, i.e. decreasing the nutrient load, is an insufficient measure to restore a nonvegetated turbid lake to a clear vegetated state. Additional measures are required for restoration, such as food Web management, i.e. removal/alteration of a part of the fish stock (biomanipulation), alteration of the water level, and sediment removal. Various models have been designed that simulate the behavior of shallow lakes and can be useful for ecosystem management, as they indicate which measures are required to improve lake transparency [36]. (B) Aβ immunotherapy has not yet proven successful in the treatment of AD. Anti-amyloid treatment only after dementia develops may be too little and too late to affect the clinical course of the disease. Similar to successful ecosystem management, multiple measures that target various disease pathways may be required to prevent or remediate AD. Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta.

processes [45]. Regional exceptions to the general model of amyloid accumulation followed by hypometabolism and atrophy were also observed in a study on autosomal dominant AD [46]. Despite the presence of amyloid deposition, it impacts the metabolism and/or atrophy differently, depending on its spatiotemporal pattern that is also related to cognitive performance [47].

Similarly, spatial heterogeneity and associated variation in the exchange of energy, species, and genotypes among habitat patches or among ecosystem subcompartments are also central to the functioning of ecosystems [48]. The impact of spatial or temporal environmental heterogeneity in an ecosystem can be illustrated by the example of eutrophication of a shallow lake (Fig. 2). Typically, the nutrient enrichment will promote algal growth that leads to increased water turbidity. With the reduced light penetration, submerged macrophyte growth and photosynthesis are reduced, which can result in a lower oxygen level in the water. Algal biomass can sediment and promote bacterial growth at the bottom of the lake, reducing the oxygen levels even more. Ultimately, this creates conditions stressful or even lethal for aquatic invertebrates and fish. Therefore, the patterns that occur during eutrophication can be considered as unfavorable to the biota.

Finally, an asymptomatic (preprodromal) phase in AD takes place whereby the first pathologic events occur without affecting the cognitive ability of the patient. At a critical point in time (threshold), a conversion takes place to mild cognitive impairment (MCI) and later to AD. In ecosystems, there is evidence that thresholds also occur and have important effects on ecosystem services [49]. An ecological threshold is the point where abrupt changes in an ecosystem property or small changes in an environmental driver produce large responses in the ecosystem. It has been suggested that ecosystems can exist in alternative stable states [50] but given enough disturbance can be pushed over the hill (i.e. threshold) to another state. Pushing back to the original state in ecosystems may require going well beyond the threshold that initiated the state transition (i.e. hysteresis).

3. Ecosystem management as a guiding principle for AD therapy design

In the past decades, significant progress has been made in understanding AD mechanisms. However, numerous clinical trials have not yet resulted in an effective AD treatment. So far, our thinking has been dominated by a linear cascade of molecular events that ultimately lead to neurodegeneration in AD. The currently available conventional therapies modulate biological processes through a single molecular target, whereas the complex and multifactorial nature of AD most likely calls for a multitarget therapeutic solution. For example, the "Aβ system" alone is already far more complex than only the prominent influence of $A\beta_{1-42}$, as subtle fluctuations of Aβ alloforms influence the trajectories through which oligomer toxicity manifests itself [23,24]. The structural aspects and time frame of existence of Aβ aggregated states are influenced by multiple variables, as opposed to a simple linear relationship. In this regard, network medicine has been suggested to offer a platform for studying both disease complexity (identifying disease factors and pathways) and the interdependencies between the different players [51]. Multitarget drugs are being developed that target various key components in AD [52] and future research and implementation of these compounds in clinical trials will reveal their potential success in the fight against AD.

We have highlighted here that for instance the behavior of Aβ in the context of AD shows many similarities with the complexity of ecosystems (Fig. 1). Other disease-contributing factors that add an extra level of complexity have been deliberately omitted from this comparison, but obviously they need to be taken into account in the future. We want to raise the awareness that ecosystem management principles may hold potential to pave the way for new insights into the neurobiological disease mechanisms and AD remediation/prevention.

A number of ecosystem management principles and paradigms may be useful to develop novel AD therapies. Promising paradigms include the notion that complex systems can exist in alternative stable states, stabilized by feedback mechanisms, and the fact that management can stimulate to reach certain favorable equilibria (Fig. 2). Additional information about temporal dynamics and alternative trajectories in complex systems can be generated by models. For instance, age-structured population models [53] developed in ecology may help to understand the evolution of molecules during the course of AD development and how this process can be influenced by changing environmental conditions. Time series data combined with trials that alternate the order of treatments/introduction of interactors in a complex system can help to assess to what extent history matters in determining the deterministic outcome of species or molecule interactions [54].

Moreover, all risk factors of AD that potentially can be modified should be identified simultaneously, so interventions can take place before the pathologic burden and neurodegeneration are irreversible (e.g. before prolonged synaptic dysfunction or accumulated cell death). In ecosystems, early warning signs for regime shifts provide a tool for the improvement of ecosystem management and serve as an indicator for the implementation of preventive actions to avoid undesirable transitions in ecosystems [55,56]. For example, microbial-based monitoring programs have been applied in the Neuse River Estuary in the United States to formulate and validate water quality models aimed at predicting nutrient productivity and algal bloom thresholds. In this context, there are indications that an impending regime shift is often announced by rapid fluctuations between the current state and a potential future stable state (flickering). For instance, clear water lakes may first become turbid for brief periods of time before they shift to a permanent turbid state [57]. Likewise, early warning signals can be predictive for transitions in type II diabetes [58] and clinical depression [59], which are clinical conditions that can be associated with AD. We need to identify thresholds and investigate the flickering of AD biomarkers in time-lapse (or so-called longitudinal) experiments (relatively well studied in autosomal dominant familial AD). The currently used cerebrospinal fluid (CSF) biomarkers reflect the core pathologic features of AD and include total tau, phosphorylated tau, and $A\beta_{1-42}$ [60]. Since the pathologic processes of AD can start even decades before the first symptoms appear, these biomarkers may provide means of early disease detection or identification of the risk for developing AD. In addition, biomarkers might prove valuable in monitoring the pharmacodynamics effect of anti-AD drugs [61]. In this way, the biochemical trajectories via which the disease manifests itself could be monitored, and controlled interventions can be made possible. This strategy is similar to how ecosystem management has been successfully applied in e.g. shallow lake restoration, where the status and nutrient loading of the lake is continuously monitored [36]. Although originally ecosystem management was mostly based on trial-and-error, it developed into an adaptive management (not only to change the system but also to learn about the system) by an in-depth monitoring of the system.

4. Conclusion

In summary, we would like to stimulate a novel way to approach AD and propose that combining network medicine with general ecosystem management principles could be a new and holistic approach to better understand AD pathology and design successful therapies. In-depth studies by combining the expertise of both researchers in the AD field

and ecologists may provide insight into the success potential of this ecosystem-based approach and its translation into concrete solutions in the future. In addition to the potential of our proposed approach to the AD field, we hypothesize that this may also impact treatment perspectives of other multifactorial neurodegenerative diseases, such as Parkinson's disease.

4.1. Recommendations and future perspectives

1. Because ecosystem management relies on the analysis of relationships between various elements in an ecosystem, lessons learned from successful ecosystem management could be applied with the aim to prevent or remediate AD. Similar to the combined set of measures necessary for the successful restoration of shallow lakes (Fig. 2A), remediation/prevention of AD may require interventions at the level of multiple disease pathways and components (Fig. 2B). For example, a recent study describes the design of a small molecule compound that targets and modulates various pathologic facets of AD, by integrating elements for Aβ aggregation control, metal chelation, reactive oxygen species regulation, and antioxidant activity [62]. This work can be an important step toward multitarget AD treatment, and clinical testing of this and other compounds will reveal their efficacy in the future. However, medication alone might not be sufficient and needs to be complemented with nonpharmacologic measures to constitute a holistic and more effective disease management strategy. Certain strategies have been shown to positively influence synaptic plasticity, such as increased fitness level through physical exercise, cognitive training or mental jogging, mindfulness, and dietary recommendations (Fig. 2B).
2. The diagnostic guidelines of AD have recently been updated to include CSF biomarkers. Biomarkers, however, cannot only be used for early detection of disease development and tracking of disease progression but also hold promise for more effective therapeutic interventions before AD progress is irreversible. Similarly to flickering in ecosystems (temporal fluctuations indicating the approach of a threshold), studies must be conducted to determine whether biomarkers also flicker, thereby announcing the conversion of for instance MCI to AD. However, this would require a more intensified monitoring and biomarker profiling of patients, not via a yearly investigation but more frequently. In conjunction with other disease progression indices (e.g. Braak staging), detailed biomarker information could then reveal particular trajectories of disease progression, thereby providing more insight into the heterogeneity of AD and allowing for disease subtyping. Ultimately, the use of biomarkers might allow for interventions tailored to the individual (i.e. personalized medicine) [61]. CSF biomarkers and pharmacodynamic markers as well as genetic markers (e.g. *APOE* genotyping) and pharmacogenomics are already fully included in innovative early phase clinical trials evaluating experimental drugs based on the amyloid cascade hypothesis. The development of behavioral (prevention) studies for cognitive decline will be of high added value for the integrated approach for supporting patients and their relatives with drugs, assisted-living tools, and real-time monitoring [63].
3. The approach presented here can also facilitate communication between different persons involved in the AD field, i.e. researchers, medical doctors, caregivers, and patients, as it offers a more convenient and tangible way to illustrate, understand, and discuss the biomolecular phenomena that occur in the brain. The ecosystem paradigm might be a powerful means to visually explain molecular aspects that occur in AD during an expert consultation. To achieve this, all people involved should be encouraged to translate the current know-how on neurobiological phenomena and AD (management) to ecosystem observations (and vice versa).
4. An interdisciplinary scientific effort focusing on treatment development, in which researchers, medical experts, and caregivers gather to reflect on the disease, is required for a deeper understanding of the underlying neurobiology of AD. The ecosystem paradigm may stimulate cross-disciplinary thinking and lead to effective dementia prevention approaches that hitherto have not yet been considered. This might lead to the development of a set of practical guidelines to be recommended to all persons involved and in particular to patients and caregivers.
5. An evaluation is required to what extent our claim holds true for all aspects of disease and ecosystem management, not to overlook potential fundamental differences, and whether other analogies may provide deeper insight. For example, contrary to species, molecules (such as Aβ) are typically not self-replicating entities. Their dynamics and turnover are determined by the surrounding tissue that produces them, rather than by differential reproductive success, migration, and mortality, as would be the case for species in an ecosystem.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2015.07.491.

RESEARCH IN CONTEXT

1. Systematic review: The authorship is multidisciplinary, consisting of biophysicists and experts in ecology and clinical neurology, using, from their respective expertise, traditional sources to review literature. We explore the parallels between the complexity of the molecular interactions within Alzheimer's disease (AD) and the complex architecture of ecosystems. Relevant literature has been appropriately cited.
2. Interpretation: By highlighting some commonalities between AD and concepts of ecosystem management, we propose that combining network medicine with general ecosystem management principles could be a new and holistic approach to understand AD pathology and design novel therapies. Our approach also offers an interesting communication tool.
3. Future directions: The development of behavioral studies for cognitive decline and the identification of early warning signals can help to predict transitions in the course of AD development. This will be of high added value for the integrated approach for supporting patients and their relatives using drugs, assisted-living tools, and real-time monitoring.

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Glossary box

Amyloid-beta (Aβ) peptide: a ∼4 kDa monomeric polypeptide that has a strong tendency to self-aggregate into oligomers and fibrils. The Aβ peptide is the main constituent of one of the main pathologic hallmarks of AD, the amyloid plaques, and plays a primary role in AD development and pathology.

Ecosystem: a dynamic and complex system comprising plant, animal, and microorganism communities with their nonliving environment interacting as a functional unit (defined here following [64]).

Ecosystem service: an activity or function of an ecosystem that provides benefit to humans (defined here following [64]).

Epigenetics: the acquired and heritable modifications on DNA that regulate the expression and functions of genes without affecting the DNA nucleotide sequence, including DNA (hydroxyl)methylation and histone modifications (defined here following [33]). Epigenetic changes are considered as a mechanism by which the environment can interact with the genome.

Eutrophication: the natural or artificial increase in nutrient load in an ecosystem and the effects of this increase on the ecosystem.

Network medicine: an integrated study of genomics, transcriptomics, proteomics, metabolomics, phenomics, and environmental perturbations, such as pharmacologic intervention or pathogenic infection, for the purpose of understanding human disease and how to cure it [51].

Patch: a relatively homogeneous subunit of an ecosystem or a spatially defined unit delineating a single ecosystem (e.g. a lake). Some ecosystems can be viewed as a mosaic of different patches, illustrating their spatial heterogeneity. Other ecosystems exist as discrete patches that may interact with the surrounding landscape matrix as well as with distant patches via dispersal and exchange of energy and matter [48].

Priority effect: this phenomenon occurs when species that arrive first in a community significantly affect the establishment, growth, or reproduction of species arriving later and thus affect community functioning. The future development of the community may thus depend on its past recruitment history and on the persistence of established residents [11].

Productivity: rate of conversion of resources into biomass, usually expressed in units of mass per unit area (volume) per unit time.