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A general neurologist’s perspective on the urgent need to apply resilience thinking to the prevention and treatment of Alzheimer’s disease

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Abstract

The goal of this article was to look at the problem of Alzheimer’s disease (AD) through the lens of a socioecological resilience-thinking framework to help expand our view of the prevention and treatment of AD. This serious and complex public health problem requires a holistic systems approach. We present the view that resilience thinking, a theoretical framework that offers multidisciplinary approaches in ecology and natural resource management to solve environmental problems, can be applied to the prevention and treatment of AD. Resilience thinking explains a natural process that occurs in all complex systems in response to stressful challenges. The brain is a complex system, much like an ecosystem, and AD is a disturbance (allostatic overload) within the ecosystem of the brain. Resilience thinking gives us guidance, direction, and ideas about how to comprehensively prevent and treat AD and tackle the AD epidemic.

Keywords: Complex system; Panarchy; Resilience thinking; Resilience; Adaptability; Transformability; Allostasis; Allostatic load; Allostatic overload

1. Introduction

1.1. There is an urgent need to address the increasing prevalence of Alzheimer’s disease

As the prevalence of Alzheimer’s disease (AD) is rapidly increasing, it is necessary and urgent to develop effective strategies for diagnosis, prevention, and treatment [1]. The cumulative effects over a patient’s lifetime and complex interactions of genetic, lifestyle, and environmental factors determine an individual’s risk for AD [2]. Buildup of amyloid-beta (Aβ) and hyperphosphorylated tau as well as neuronal degeneration, blood-brain barrier pathology, neuroinflammation, oxidative stress, and microvascular, cytoskeleton, and mitochondrial changes are responsible for AD development [3]. Given the multifactorial etiology of AD, it is important to consider use of comprehensive, life course approaches to prevent and treat this disease, and pay more attention to the multiple risk factors of AD such as coronary artery disease, diabetes, hypertension, obesity, cancer [2,4], environmental pollution [5,6], cigarette smoking, and chronic stress [7–9]. As chronic diseases (e.g., insulin resistance and diabetes) are on the rise, the prevalence of AD is expected to increase. There is evidence that neuroinflammation and oxidative stress, linked to environmental pollution, unhealthy diet, disturbance in gut-microbiota [10], and stress, are all common denominators for the aforementioned chronic conditions and dementia. Thus, it makes sense that reducing chronic inflammatory responses and oxidative stress [11,12] by lifestyle changes (e.g., promoting healthy nutrition, exercise, stress management) should become a focus of prevention and treatment of AD. Given the multifactorial nature of AD, collaboration and teamwork between neurologists, geriatricians, primary care providers, social workers, nutritionists, and psychologists need to take place to understand and treat the whole patient rather than each condition separately.

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2352-8737/© 2017 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer’s Association. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Another problem that we face in the AD epidemic is the declining number of neurologists [13] due to the decreased interest of medical students in this specialty and increased burnout of neurologists who subsequently cut down on their number of working hours or leave their specialty altogether. Given this, the number of neurological patients (including those with AD) who are underdiagnosed and undertreated is going to increase. Addressing burnout among neurologists and all physicians is an urgent problem to be solved in the era of a worsening epidemic of chronic diseases. Caregiver burnout also is on the rise, leading to an increase in stress-related chronic conditions among caregivers, another challenging and important problem that requires urgent solutions.

Focusing research on elimination of amyloid plaques and neurofibrillary tangles is not enough to tackle the epidemic of AD without enhancing our population’s vitality, resilience, social connectivity, and addressing environmental and social issues. AD is a complex problem that needs to be viewed on many different levels and scales, such as the individual patient, health care, family, and society. Biological, psychological, sociological, and technological contexts also need to be taken under consideration.

This perspective is written from the point of view of a general neurologist and proposes merging a holistic approach to a patient with AD with the approach of a clinician specializing in dementia research. The authors (the second author is a psychologist who is very familiar with the socioecological model) feel that both approaches are equally necessary: in the holistic approach, the patient is treated as a unique and interconnected system, embedded within its context; in the clinical specialists’ approach that is based on research of the disease, important generalizations and conclusions about AD pathophysiology and natural history are uncovered. In this perspective, the authors address merging a practical approach with theoretical research because of the growing epidemic of the disease, lack of effective treatments, urgency, and angst to find solutions. The authors are part of interconnected systems forming the health care system that include specialists, psychologists, geriatricians, primary care providers, nutritionists, nurses, and staff, whose goal is to address not only a disease but also problems related to it. Because AD is a complex disease affecting all aspects of a person’s life, it is essential for the health care system and its parts to communicate, act in unison, recognize, and address those challenges.

2. Method: Review of literature on resilience concepts and resilience thinking

2.1. Resilience research and resilience thinking in health sciences

Resilience thinking originated in ecology [14] and includes the concepts of resilience, adaptability, and transformability [15]. These emerging phenomena characterize the nature of a complex system and its behavior. Resilience is the capacity of socioecological systems to continually change and adapt while remaining within critical thresholds [16,17]. Adaptability is the capacity of the system to learn, use experience and knowledge, adjust to a changing environment, and continue to develop within critical thresholds. Transformability is the capacity to cross thresholds into new developmental trajectories to create a fundamentally new system when ecological, economic, or social structures make the existing system untenable [15]. Resilience thinking describes a natural, self-evolving, and self-emerging process in all complex systems. It represents a theoretical framework that emerged out of the observations that an ecosystem can thrive while undergoing transformations in response to stress [17].

2.2. Complex systems in resilience thinking

Research in socioecology reveals that we live in multiple complex systems and that complex systems interact with each other and form subsystems of larger systems, a concept known as panarchy [18]. Panarchy takes into consideration the cross-scale, cross-disciplinary, dynamic, and unpredictable nature of complex systems [14]. A complex system consists of agents that interact with each other in a random way (e.g., organisms, neurons) and out of that interaction patterns arise that send feedback to the agents, modulating their behavior [19]. The boundaries of complex systems are arbitrary because the system interacts and often merges with other systems and the environment. The choice of complex system boundaries will determine which agents (components or species) and interactions are analyzed [3]. Examples of complex systems are numerous and include the universe, climate, ecosystem, social organization, community, family, health care system, patient, doctor, brain, or individual cell.

Over time, a complex system changes shape, transforms, and self-evolves in response to the environment, so it must be studied within its context and other interconnected systems. It is never in perfect equilibrium but rather fluctuates between critical thresholds. It may even pass a threshold and become a new system. The driving force is the resilience of the system that moves it forward. The system absorbs the stress, adapts, and changes its shape in response to a constantly changing environment with which the complex system coevolves [17]. Any complex system goes through adaptive cycles and fluctuates between states of growth and collapse [14,16].

2.3. Allostasis: Mechanisms of adaptation in response to stress

Resilience thinking is not only about bringing the system back to balance but also about moving beyond thresholds and developing a new balance (regime shift) in response to challenges. Stress and resilience are tightly linked and influence each other [20]. Resilience incorporates stress or
2.4. Resilience thinking in health sciences

Although resilience thinking originated in ecology, it has extended to other areas, such as health care. Resilience thinking applied to the field of health sciences includes the concept of allostasis, attractor basins (the conceptual space in which the dynamic system resides over time), and thresholds within which every complex system operates [22]. Resilience research in health sciences has evolved over the years. Although many definitions of resilience exist in health sciences, the consensus is that resilience can be viewed as a trait (resiliency or ego-resiliency), process, or outcome. It exists on a continuum, varies across different domains, and can change depending on context [23–25]. The following definitions capture the essence of resilience in health sciences: “A reintegration of self that includes a conscious effort to move forward in an insightful integrated positive manner as a result of lessons learned from an adverse experience” [24]; “the capacity of individuals, families, communities, systems, and institutions to anticipate, withstand, or judiciously engage with catastrophic events or experiences” [26]; and “resilience can be broadly defined as the capacity of a dynamic system to adapt successfully to disturbances that threaten system function, viability, or development” [27]. Resilience understood in this way is identical to the concept of resilience thinking derived from socioecology [15] that includes an understanding of the adaptive cycle [28] in which resilience, adaptability, and transformability (resilience, adaptability, and transformability) describe the nature of any complex adaptive system, such as the brain network. Remodeling of the brain network is equivalent to adaptability, whereas neuroplasticity is equivalent to transformability leading to resilience of the system. They reflect the capacity of any system to change and adapt to stressful conditions. Brain circuitry can be remodeled in response to stress, resulting in neuroplasticity [32]. Changes not only in the outside environment but also within the brain structure due to aging trigger functional adaptations. A general feature of the brain is the ability to adapt to structural alterations by engaging in functional reorganization, or in other words developing compensatory networks when the primary networks are impaired [33]. The brain is an efficient and adaptive learner [34]. Active coping is a healthy stress response and dynamic neural activity during stress signals resilient coping [35]. Although the concepts of resilience in AD research are constantly evolving and it is difficult to measure cognitive reserve [29,33,36], there is evidence that unifying concepts and theories that describe a variety of complex adaptive systems, and that share resilience as a common feature, have been increasingly applied to neuroscience research. These unifying theories using mathematical equations to describe system dynamics are applied to various contexts (social, technological, informational, and biological) [37]. They discuss the interactions among many interconnected elements leading to complex system behaviors resulting in resilience of the system. The problems they address provide fundamental explanations.
for the emergence of complex system behavior from the inter-
action of its parts. The translation of these approaches to the

cognitive and clinical neurosciences may be crucial to address
challenges in these fields and address resilience research in
AD. Complex network mathematical models, such as graph
theoretical analysis of structures (diffusion tractography or
cortical thickness/volume correlation), and functional mag-
netic resonance imaging provide new measures of human
brain organization showing that the whole brain network
exhibits properties shared with many other complex systems
[38,39]. They also provide new insights into the pathophysiology of many neurological and psychiatric
diseases such as AD, stroke, tumors, multiple sclerosis,
epilepsy, schizophrenia, autism, and attention-deficit/
hyperactivity disorder [38].

2.6. Addressing AD from a perspective of resilience
thinking

Depending on the level of resilience, pathological changes
of AD might be more or less challenging and be time depen-
dent for any given person. Because resilience exists on a con-
tinuum, it would explain the observations that risk factors for
AD might have a different impact across an individual’s life-
span. Any intervention that fosters resilience would likely in-
crease a person’s brain’s ability to cope and adapt to the
challenges related to AD pathology. These interventions also
are likely to differ for each person and differ in the same person
across their lifespan [25]. The process of neuroplasticity and
neurogenesis may take a long time. If we want to address
the epidemic of AD, it is necessary to understand that the dis-
ease develops over many years, even decades, so the factor of

The increasing prevalence of AD is intriguing. It is clear
that an aging population is not the only reason. Resilience
thinking allows seeing AD in a comprehensive way, unveils-
ing that AD is linked to an intricate web of many factors over
a long period. Some of these factors are not clearly evident.
AD is the result of interactions between certain susceptibility
genes, environmental factors, and lifestyle [3]. To better treat
and prevent AD, an understanding is required of how much
each factor contributes to the development of the disease, at
what point in life each factor has the most impact on the in-
dividual, and the context within which each person lives. It is
the authors’ view that the increasing prevalence of AD is
often a reflection of unhealthy environments and lifestyle
in our modern society. The examples of nongenetic factors
that could contribute to development of AD include the
following: (1) a high-sugar diet and the increased use of an-
tibiotics that change the microbiome in the gut leading to
inflammation and insulin resistance; (2) an increasingly
stressful lifestyle, isolation, and lack of meaning and pur-
pose that may cause mental health disorders such as anxiety,

3. Application

3.1. Arguments for applying resilience thinking to the
prevention and treatment of Alzheimer’s disease

Resilience thinking provides a framework for under-
standing and describing naturally emerging phenomena (re-
silience, adaptability, and transformability) that occur in
stressful conditions in all complex systems. It is a theory
that helps us understand how these systems function, in the
same way that mathematics or physics helps us understand
processes that happen in nature. Resilience thinking is
born in complex, nonlinear, dynamic, interconnected sys-
tems such as a socioecological system in which the health
care system is included. Knowledge about the nature of a
complex system and its emerging phenomena may be
applied to every complex system (such as the brain and hu-
man health) because it reflects the nature of these systems.
By understanding the connections between our health and
ecosystem, as well as other interconnected systems, we
can start linking seemingly unrelated phenomena across
different domains. Resilience thinking can be used as a
lens to look at any chronic disease and, from a general neu-
rologist’s perspective, to control the AD epidemic.

3.1.1. The AD epidemic: Multiple contributing factors

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stressful lifestyle, isolation, and lack of meaning and pur-
pose that may cause mental health disorders such as anxiety,
and effective strategies to promote prevention are required. Although we might never find a cure for AD, we can work toward finding ways to prevent it. An outstanding example of how this might happen is the Nun Study. In this study, despite pathological changes of AD in the brain, many nuns did not show any clinical signs of the disease indicating that their brains may be resilient to AD pathology [48–51]. Asymptomatic state of Alzheimer’s disease is the presence of AD pathology in individuals with no clinical signs of the disease [1]. Cognitive reserve in these individuals allows them to function cognitively. It is a resilience factor [48,52] that allows for healthy aging [53] and prevents clinical signs of AD despite neuropathology [30,54–57]. Higher cognitive function and cognitive reserve may be protective against AD. People who cultivate resilience may be less likely to develop signs of AD and be able to cope with stress and disease better than those who do not. In many cases of AD, the previous balance most likely will never be reached; however, reaching a new balance that allows the person to function cognitively is still possible despite significant brain pathology. Although a cure for AD might not be possible and treatment becomes increasingly more challenging in advanced stages of the disease, resilience of human spirit is possible even until the end [53].

3.1.4. An essential role for resilience in today’s modern world

Humans lead increasingly stressful lives [24] in an increasingly complex world. In the past, the main stressors that humans struggled with were to figure out how and where to find food or shelter and how to escape danger. The biological mechanisms responsible for allostatics that our brain and body use are in fact ancient and have not changed much since the beginning of the human species. We use the same mechanisms that our ancestors used although their environment was completely different from ours. Over the past 100 years, we have been living in a fast developing modern human society with drastically different lifestyles [21]. It is characterized by overwork, high consumption of fast food, decreased physical activity, nature deprivation, environmental pollution, and disruption of the sleep-wake cycle. This modern lifestyle leads to allostatic load and overload that have a negative impact on physical and mental health [21] and has been associated with many chronic diseases including AD. On top of that, we face a rapidly enlarging population, climate change, and social conflicts that add to an already existing stressful lifestyle. Individual and social problems (including the AD epidemic) become increasingly more complex and require systemic thinking, such as resilience thinking, to understand, approach, and solve these problems.

3.1.5. Resilience thinking: Applying a positive approach to AD prevention and treatment

Resilience is a concept that provides a positive focus on vitality and disease. This is contrary to the current medical model that focuses on deficit and disease and was summarized by Southwick et al. as follows:
Rather than spending the vast majority of their time and energy examining the negative consequences of trauma, clinicians and researchers can learn to simultaneously evaluate and teach methods to enhance resilience. Such an approach moves the field away from a purely deficit based model of mental health, toward the inclusion of strength and competence-based models that focus on prevention and building strengths in addition to addressing psychopathology [24].

A change from deficit-focused health care to vitality-focused health care in dealing with chronic diseases is necessary and inevitable. The current health care system cannot solve health problems linked to the following issues: job loss, lack of housing and poverty, social isolation, nature and human contact deprivation, social conflicts, lack of education, environmental pollution, natural disasters, climate change, unhealthy diet, and overuse of antibiotics. Understanding the interaction between multiple interconnected systems and interdisciplinary cross-scale approaches are required. An innovative, integrative, systemic, and holistic approach is necessary in today’s interconnected and complex world.

4. Conclusions

The nature of complex systems is to produce emergent phenomena such as resilience, adaptability, and transformability. Any complex system, such as an ecosystem, brain, body, individual, family, society, population, and socioecological system, interacts and responds to the surrounding environment, and is shaped by it. Any complex system is capable of thriving in response to challenges.

The resilience of an individual person and a person’s brain depends on many factors and exists on many levels. To understand resilience of the brain, it is helpful to view the brain as a complex system embedded within the context it resides in and connected to other complex systems within the body and outside of the body by feedback loops. It is also important to see the brain as a system that is constantly adapting to the environment in the process of neuroplasticity and neurogenesis in response to challenges. Therefore, it is important to study the brain and its function within an individual context to prevent and treat diseases, such as AD, that may affect this system.

Neuroplasticity and neurogenesis are processes analogous to the phenomena responsible for adaptation and transformation of an ecosystem. If the brain is viewed as an ecosystem, enhancement of brain resilience is analogous to cultivation of ecosystem sustainability (ecosystem management). Words often used in resilience research include abundance and flexibility. The more diverse, flexible, and open the complex system is, the more resilient it is. The abundance of synaptic connections and the redundancy of the brain’s anatomical and functional architecture [31] give rise to cognitive reserve. AD is understood as a disturbance or disequilibrium (allostatic overload) within the ecosystem of the brain. Clinical signs of AD occur if the brain can no longer cope and adjust to the changes (allostatic overload).

After many years of research, we still do not fully understand the mechanisms and pathophysiology of AD and why some people, despite AD pathology, do not have signs of the disease. In the meantime, the prevalence of the disease is reaching epidemic proportions calling for possible interventions. As we noted previously, some of the answers can come from socioecological resilience thinking that is applied to ecosystem management, in which not fully understanding how the system works and trying new practical solutions, taking risks, and being prepared to fail is an acceptable approach [14]. Even if research does not clearly demonstrate what the risks and protective factors of AD are, it is reasonable to apply interventions that may or may not turn out to be helpful but are not harmful. There is “nothing to lose” and “there is no harm” in healthy eating, maintaining a healthy sleep-wake cycle, cultivating relationships, increasing education, exercise, stress management, practicing mindfulness, finding meaning and purpose, and developing spirituality. In fact, we see benefits of these interventions on reducing brain allostatic load and cognitive enhancement. Recent findings show that occupational complexity [58–60], busy schedule [61,62], multilingualism [63,64], music [65], physical activity [66,67], or mindfulness-based interventions [68] may improve cognition, promote brain plasticity, and reduce risk of dementia and AD. We cannot afford to delay prevention and potential treatment as AD and other chronic diseases are on the rise, contributing to the increased cost and health care crisis. Even if these potential protective factors do not prevent or treat AD, they may prevent development of other chronic diseases often linked to AD and improve the health, well-being, vitality, and resilience of AD patients.

Applying current research on AD and resilience thinking to individuals appears to be a comprehensive and probably the most effective way to approach AD, providing practical tools and solutions. Waiting for a cure is not a solution in the era of the AD epidemic. Action is needed now.

This perspective is unique because it provides a comprehensive, broad, and in-depth view of cognition, cognitive reserve, and cognitive resilience that is applicable not only to AD but also to any brain insult or neurodegenerative condition. We provide both a macroperspective and microperspective by connecting knowledge from a variety of fields: from complex adaptive systems and network science through socioecology and cognitive science. It illustrates that the brain is a complex adaptive system whose intrinsic nature is resilience through adaptation and transformation. The authors recognize patterns across all complex adaptive systems and present an exploration across fields with a variety of sources cited. Our article combines the perspectives of a general neurologist with a behavioral and cognitive psychologist, using an approach that is both theoretical and practical with important information and recourses for patients, caregivers, providers, and scientists. In the era of increased specialization, health care often becomes
fragmented, addressing organs of a human body rather than the whole patient. A generalized view with broad awareness is as important as a specialized view with both views providing complementary and vital information. This article calls for a comprehensive approach to AD in an era of increased specialization to avoid fragmentation of medical fields and sciences.

5. Implications of this research

A socioecological framework of resilience thinking has applications in health because ecosystems and health are interconnected (ecohealth) [69–71].

Through this work, the definition of resilience becomes unified. Resilience concepts and resilience thinking can be used across different domains: from socioecological systems to health care. It provides a new, broad, and in-depth approach to any chronic disease. Rather than just treating symptoms, we should be focusing on understanding the root causes of different symptoms and diseases, and approaching the patient holistically. The concept of resilience applies to every patient with complex and chronic medical problems. Given that humans are complex organisms forming interconnected systems with nature and other systems such as industry or technology [72], resilience thinking can provide a useful approach. It is a universal approach by which all complex systems can function in harmony to create a sustainable system.

This perspective of resilience thinking can have a strong public health impact [47]. We do not have effective cures for neurodegenerative diseases such as AD. The treatments that are available only address the symptoms at best. Because prevention is the best treatment, understanding root causes of AD is crucial to prevent this disease. Resilience thinking takes into consideration processes and factors seemingly unrelated to each other and investigates potential connections between genetics, lifestyle, and the environment. Researching the link between AD and chronic diseases, such as diabetes, cancer, and cerebrovascular disease as well as the environment, industry, technology, and global health to AD, will give us a better understanding of the causes and strategies to prevent and treat this disease [4]. In addition, this work directs attention to the caregiver’s roles and needs [73]. It recognizes burnout and calls for fostering resilience among neurologists [74] and other health care providers because their health is essential for providing high-quality and safe patient care.

Resilience concepts and systemic resilience thinking broadens our understanding of the links between lifestyle, environment, ecosystem, and health. By linking the ecosystem and health care system, we can create a sustainable socioecological health care system that allows people and nature to coexist and thrive. Use of resilience thinking is fundamental to the creation of an integrated health care system with a focus on vitality and resilience that will lead to improved health and well-being of patients, providers and caregivers while decreasing medical errors and reducing health care costs.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the current literature in PubMed focusing on articles related to stress and disease, applications for resilience thinking, and Alzheimer’s disease (AD). A complex systems approach combined with resilience thinking has not been widely used to understand the pathophysiology of AD or to prevent and treat this devastating disease. To demonstrate the importance of this approach to AD, we summarize the relevant literature and expand on the benefits of applying this approach to AD research.

2. Interpretation: Our review supports a multidisciplinary approach in which resilience thinking is applied to address many factors leading to AD. This approach is consistent with findings currently in the public domain.

3. Future directions: The article advocates an integrated health care system with a focus on vitality and resilience that will lead to improved health and well-being of patients, providers, and caregivers; decrease medical errors; and reduce health care costs.

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