11-1-2017

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

Grazyna Pomorska
University of Massachusetts Medical School

Judith K. Ockene
University of Massachusetts Medical School

Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 498-506

Perspective

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

Grazyna Pomorska[a,*], Judith K. Ockene[b]

[a]Department of Neurology, University of Massachusetts Memorial Medical Group, Worcester, MA, USA
[b]Department of Medicine, Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School, Worcester, MA, USA

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.

*Corresponding author. Tel.: 508-334-6641; Fax: 508-334-9034.
E-mail address: Grazyna.Pomorska@umassmemorial.org

http://dx.doi.org/10.1016/j.trci.2017.08.001

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

disease and transforms a complex system in such a way that it is able to adapt, or even thrive in new (or stressful) conditions. Researchers developed the concept of allostasis to describe mechanisms that take place during the process of adaptation [21]. Allostasis is defined as a successful adaptation or dynamic control over perturbations for maintaining a functional state [20]. Dysregulation of the systems responsible for allostasis may lead to allostatic overload and cumulative damage [21], presenting as atherosclerosis, obesity, glucose dysregulation, psychiatric disorders, and brain atrophy (among others).

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 [16] takes place in response to stressful challenges. Resilience researchers in health sciences came to the conclusion that to understand resilience and apply the concept of resilience in a particular domain, an interdisciplinary approach is necessary [24] and "the concept can be applied to systems of many kinds at many interacting levels, both living and nonliving, such as a microorganism, a child, a family, a security system, an economy, a forest, or the global climate" [27]. Thus, applying resilience thinking to additional disciplines (e.g., neuroscience) is warranted.

2.5. Resilience thinking in neuroscience

In our view, resilience thinking is also present in neuroscience; an analogous phenomenon that leads an ecosystem to change shape occurs in the brain in response to stress. The brain is the crucial organ in maintaining allostasis for the whole body and adaptive plasticity to signals that it receives. It has the capacity to adapt despite high levels of stress and its effects. The brain determines whether adaptation will be successful (allostasis) or lead to cumulative damage or pathophysiology (allostatic overload) [21]. Challenging, but not destructive, stress enhances learning and neuroplasticity. A challenge to be overcome, as long as it does not cause damage or allostatic overload (*U*-shaped relationship between stress and cognition), is the driving force for the brain to learn by forming new synaptic connections (neuroplasticity) or generating new neurons (neurogenesis). In a healthy or damaged brain, learning continues and new neurons or pathways can still be formed. New synaptic connections emerge, and damaged pathways that served certain functions are replaced by new pathways. Neuroplasticity occurs across an individual's lifespan [20], even in AD. The inability to use synaptic connections due to pathological changes in AD challenges neurons to form new connections and a new structure emerges [29,30] that is unique to each individual. In addition, functional organization within brain networks changes in response to AD pathology leading to decoupling of structure and function [31].

We deduced that learning and neuroplasticity are analogous to the naturally emerging process that occurs in socioecological systems characterized by resilience, adaptability, and transformability in response to challenge—the fundamental aspects of resilience thinking. These terms (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 interaction 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 magnetic 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 dependent for any given person. Because resilience exists on a continuum, it would explain the observations that risk factors for AD might have a different impact across an individual's lifespan. Any intervention that fosters resilience would likely increase 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 disease develops over many years, even decades, so the factor of time needs to be included in prevention and treatment.

To address AD and its epidemic, it is necessary to look at many contributing factors, not just the disease itself, but also the whole patient and his/her environment, caregiver, provider, health care system, and other interconnected systems, which is summarized in the following excerpt from Southwick et al.:

> In order to develop effective interventions to enhance resilience, it is critical to understand that humans are embedded in families, families in organizations and communities, and communities in societies and cultures. Interventions targeted at any one of these levels will impact functioning at other levels [24].

Humans represent complex systems on many different levels, such as biological and socioecological, and human health is linked to other organisms within the network of populations, communities, and ecosystem interactions [40]. Taking this a step further, human health needs to be viewed in the context of global ecosystems that are defined as dynamic and complex aggregations of communities constantly adapting to internal and external influences. In addition, we cannot forget about the impact and influence of technology on the socioecological system including health care. Technology and society are interdependent and evolve together. Our culture is shaped by technology. Fast development of technology can have unpredictable positive and negative impacts on prevalence and management of AD. Sociocultural change in the era of the Internet may lead in some cases to isolation and loneliness-risk factors for dementia [41,42]. Assistive technology, on the other hand, can help patients with dementia in their daily activities and improve their safety [43]. Constantly evolving technology in the health care system can be both cumbersome and effective in the management of patients with dementia.

3. Application

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

Resilience thinking provides a framework for understanding and describing naturally emerging phenomena (resilience, 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 systems 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 human 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 neurologist's perspective, to control the AD epidemic.

3.1.1. The AD epidemic: Multiple contributing factors

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, unveiling 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 individual, 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 antibiotics that change the microbiome in the gut leading to inflammation and insulin resistance; (2) an increasingly stressful lifestyle, isolation, and lack of meaning and purpose that may cause mental health disorders such as anxiety,

depression, and substance abuse (without addressing mental health issues, the prevalence of neuropsychiatric disorders and other chronic diseases is going to rise [44]); and (3) an increasing amount of toxins and chemicals in the environment that may lead to neurotoxicity and neurodegenerative disorders [45]. It is also possible that the interplay between all these factors causes allostatic load and overload within susceptible individuals leading to AD.

3.1.2. Chronic diseases associated with AD

In recent years, the connections between many chronic diseases and neurodegenerative diseases (including AD) have been recognized. The type of associated chronic disease may give us a clue to the potential cause of AD and lead us to administer appropriate and feasible interventions, such as reducing chronic inflammation by restoration of the gut microbiome, preventing and treating insulin resistance and diabetes [4] through healthy diet, and reducing stress and regulating allostasis [32,46] through mindfulness. Restoring a healthy sleep-wake cycle, social integration [32], and helping people find meaning and purpose are also important interventions in the treatment of chronic diseases, such as AD. This broad and holistic perspective might change the way we think of AD and other chronic diseases.

Understanding links between different diseases also has an impact on preventive strategies. Given that AD currently is a noncurable disease, increased focus on prevention is an important, if not the most important approach. Our short-term thinking of a quick fix and suppression of symptoms in chronic diseases rather than searching for the root causes of the disease creates unhealthy populations and an unsustainable, increasingly expensive health care system. We need to look at it from multiple angles and work on addressing all the potential factors to determine the contribution of each factor to the development of AD in any particular individual. AD may in fact have unique causes for each patient and needs to be approached at an individual level to understand the etiology and to develop personalized treatment. This is an argument to emphasize disease prevention and promote personalized and individualized health care.

3.1.3. Preventing AD through enhancing an individual's resilience

How a person copes with AD pathology depends on the health and resilience of the individual's mind, body, and spirit. Resilience thinking explains the nature and potential of every complex system such as a human being. Everyone and every brain are capable of adaptation and transformation in response to stress and challenge. Individual resilience depends on all the interconnections between systems in which we are embedded [47], such as family, community, society, and environment. Fostering resilience, therefore, needs to focus on different levels of relationships and interconnections between these interacting systems [24]. To tackle the AD epidemic, individual and collective resilience is needed, 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 allostasis 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.

References

[1] Driscoll I, Troncoso J. Asymptomatic Alzheimer's disease: a prodrome or a state of resilience? Curr Alzheimer Res 2011; 8:330–5.
[2] Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci 2009;11:111–28.
[3] Hubin E, Vanschoenwinkel B, Broersen K, De Deyn PP, Koedam N, van Nuland NA, et al. Could ecosystem management provide a new framework for Alzheimer's disease? Alzheimer's Dement 2016; 12:65–74.e1.
[4] Jabir NR, Firoz CK, Baeesa SS, Ashraf GM, Akhtar S, Kamal W, et al. Synopsis on the linkage of Alzheimer's and Parkinson's disease with chronic diseases. CNS Neurosci Ther 2015;21:1–7.
[5] Yegambaram M, Manivannan B, Beach TG, Halden RU. Role of environmental contaminants in the etiology of Alzheimer's disease: a review. Curr Alzheimer Res 2015;12:116–46.
[6] Weuve J. Invited commentary: how exposure to air pollution may shape dementia risk, and what epidemiology can say about it. Am J Epidemiol 2014;180:367–71.
[7] Rothman SM, Mattson MP. Adverse stress, hippocampal networks, and Alzheimer's disease. Neuromolecular Med 2010;12:56–70.
[8] Tatomir A, Micu C, Crivii C. The impact of stress and glucocorticoids on memory. Clujul Med 2014;87:3–6.

[9] Tran TT, Srivareerat M, Alkadhi KA. Chronic psychosocial stress triggers cognitive impairment in a novel at-risk model of Alzheimer's disease. Neurobiol Dis 2010;37:756–63.
[10] Catanzaro R, Anzalone M, Calabrese F, Milazzo M, Capuana M, Italia A, et al. The gut microbiota and its correlations with the central nervous system disorders. Panminerva Med 2015;57:127–43.
[11] Naseer MI, Bibi F, Alqahtani MH, Chaudhary AG, Azhar EI, Kamal MA, et al. Role of gut microbiota in obesity, type 2 diabetes and Alzheimer's disease. CNS Neurol Disord Drug Targets 2014; 13:305–11.
[12] Numan MS, Brown JP, Michou L. Impact of air pollutants on oxidative stress in common autophagy-mediated aging diseases. Int J Environ Res Public Health 2015;12:2289–305.
[13] Bianchi R. Physician burnout: A neurologic crisis. Neurology 2015; 84:2098.
[14] Curtin CG, Parker JP. Foundations of resilience thinking. Conserv Biol 2014;28:912–23.
[15] Folke C, Carpenter S, Walker B, Scheffer M, Chapin T, Rockström J. Resilience thinking: integrating resilience, adaptability and transformability. Ecol Soc 2010;15:20.
[16] Walker B, Holling CS, Carpenter S, Kinzig A. Resilience, adaptability and transformability in social–ecological systems. Ecol Soc 2004;9:5.
[17] Berkes F, Doubleday NC, Cumming GS. Aldo Leopold's land health from a resilience point of view: self-renewal capacity of social-ecological systems. Ecohealth 2012;9:278–87.
[18] Benson MH, Garmestani AS. Embracing panarchy, building resilience and integrating adaptive management through a rebirth of the National Environmental Policy Act. J Environ Manage 2011;92:1420–7.
[19] Odell J. Agents and complex systems. J Object Technology 2002; 1:35–45.
[20] Franklin TB, Saab BJ, Mansuy IM. Neural mechanisms of stress resilience and vulnerability. Neuron 2012;75:747–61.
[21] Karatsoreos IN, McEwen BS. Psychobiological allostasis: resistance, resilience and vulnerability. Trends Cogn Sci 2011;15:576–84.
[22] Oken BS, Chamine I, Wakeland W. A systems approach to stress, stressors and resilience in humans. Behav Brain Res 2015; 282:144–54.
[23] Pietrzak RH, Southwick SM. Psychological resilience in OEF-OIF Veterans: application of a novel classification approach and examination of demographic and psychosocial correlates. J Affect Disord 2011; 133:560–8.
[24] Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: interdisciplinary perspectives. Eur J Psychotraumatol 2014;5.
[25] Reich JW, Zautra AJ, Hall JS. Handbook of Adult Resilience. New York: Guilford Press; 2010.
[26] Almedom AM, Tumwine JK. Resilience to disasters: a paradigm shift from vulnerability to strength. Afr Health Sci 2008;8:S1–4.
[27] Masten AS. Global perspectives on resilience in children and youth. Child Dev 2014;85:6–20.
[28] Fath B, Dean C, Katzmair H. Navigating the adaptive cycle: an approach to managing the resilience of social systems. Ecol Soc 2015;20.
[29] Jellinger KA, Attems J. Neuropathological approaches to cerebral aging and neuroplasticity. Dialogues Clin Neurosci 2013;15:29–43.
[30] Negash S, Wilson RS, Leurgans SE, Wolk DA, Schneider JA, Buchman AS, et al. Resilient brain aging: characterization of discordance between Alzheimer's disease pathology and cognition. Curr Alzheimer Res 2013;10:844–51.
[31] Rudrauf D. Structure-function relationships behind the phenomenon of cognitive resilience in neurology: insights for neuroscience and medicine. Adv Neurosci 2014;2014:28.
[32] McEwen BS, Gianaros PJ. Stress- and allostasis-induced brain plasticity. Annu Rev Med 2011;62:431–45.
[33] Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. Trends Cogn Sci 2013;17:502–9.
[34] Deneve S, Alemi A, Bourdoukan R. The brain as an efficient and robust adaptive learner. Neuron 2017;94:969–77.
[35] Sinha R, Lacadie CM, Constable RT, Seo D. Dynamic neural activity during stress signals resilient coping. Proc Natl Acad Sci U S A 2016; 113:8837–42.
[36] Jones RN, Manly J, Glymour MM, Rentz DM, Jefferson AL, Stern Y. Conceptual and measurement challenges in research on cognitive reserve. J Int Neuropsychol Soc 2011;17:593–601.
[37] Medaglia JD, Pasqualetti F, Hamilton RH, Thompson-Schill SL, Bassett DS. Brain and cognitive reserve: translation via network control theory. Neurosci Biobehav Rev 2017;75:53–64.
[38] Guye M, Bettus G, Bartolomei F, Cozzone PJ. Graph theoretical analysis of structural and functional connectivity MRI in normal and pathological brain networks. MAGMA 2010;23:409–21.
[39] Gong G, He Y, Concha L, Lebel C, Gross DW, Evans AC, et al. Mapping anatomical connectivity patterns of human cerebral cortex using in vivo diffusion tensor imaging tractography. Cereb Cortex 2009; 19:524–36.
[40] Kearns A, Beaty M, Barnett G. A social–ecological perspective on health in urban environments. N S W Public Health Bull 2007; 18:48–50.
[41] Rafnsson SB, Orrell M, d'Orsi E, Hogervorst E, Steptoe A. Loneliness, social integration, and incident dementia over 6 years: prospective findings from the English Longitudinal Study of Ageing. J Gerontol B Psychol Sci Soc Sci 2017; http://dx.doi.org/10.1093/geronb/gbx087 [Epub ahead of print].
[42] Poey JL, Burr JA, Roberts JS. Social connectedness, perceived isolation, and dementia: does the social environment moderate the relationship between genetic risk and cognitive well-being? Gerontologist 2017;57:1031–40.
[43] Kenigsberg PA, Aquino JP, Berard A, Bremond F, Charras K, Dening T, et al. Assistive technologies to address capabilities of people with dementia: from research to practice. Dementia (London) 2017. 1471301217714093.
[44] Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. Lancet 2007;370:859–77.
[45] Costa LG, Cole TB, Coburn J, Chang YC, Dao K, Roque PJ. Neurotoxicity of traffic-related air pollution. Neurotoxicology 2017;59:133–9.
[46] Hasegawa T. Prolonged stress will induce Alzheimer's disease in elderly people by increased release of homocysteic acid. Med hypotheses 2007;69:1135–9.
[47] Castleden M, McKee M, Murray V, Leonardi G. Resilience thinking in health protection. J Public Health (Oxf) 2011;33:369–77.
[48] Snowdon DA. Healthy aging and dementia: findings from the Nun Study. Ann Intern Med 2003;139:450–4.
[49] Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR. Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. Neurobiol Aging 2005;26:341–7.
[50] Iacono D, Markesbery WR, Gross M, Pletnikova O, Rudow G, Zandi P, et al. The Nun study: clinically silent AD, neuronal hypertrophy, and linguistic skills in early life. Neurology 2009;73:665–73.
[51] SantaCruz KS, Sonnen JA, Pezhouh MK, Desrosiers MF, Nelson PT, Tyas SL. Alzheimer disease pathology in subjects without dementia in 2 studies of aging: the Nun Study and the Adult Changes in Thought Study. J Neuropathol Exp Neurol 2011;70:832–40.
[52] Wook Yoo S, Han CE, Shin JS, Won Seo S, Na DL, Kaiser M, et al. A network flow-based analysis of cognitive reserve in normal ageing and Alzheimer's disease. Sci Rep 2015;5:10057.
[53] Harris PB. Another wrinkle in the debate about successful aging: the undervalued concept of resilience and the lived experience of dementia. Int J Aging Hum Dev 2008;67:43–61.
[54] Negash S, Xie S, Davatzikos C, Clark CM, Trojanowski JQ, Shaw LM, et al. Cognitive and functional resilience despite molecular evidence of Alzheimer's disease pathology. Alzheimer's Dement 2013;9:e89–95.
[55] Salmond CH, Menon DK, Chatfield DA, Pickard JD, Sahakian BJ. Cognitive reserve as a resilience factor against depression after moderate/severe head injury. J Neurotrauma 2006;23:1049–58.

[56] Perneczky R, Alexopoulos P, Schmid G, Sorg C, Forstl H, Diehl-Schmid J, et al. Cognitive reserve and its relevance for the prevention and diagnosis of dementia. Nervenarzt 2011;82:325–30, 332-335.
[57] Noppeney U, Friston KJ, Price CJ. Degenerate neuronal systems sustaining cognitive functions. J Anat 2004;205:433–42.
[58] Boots EA, Schultz SA, Almeida RP, Oh JM, Koscik RL, Dowling MN, et al. Occupational complexity and cognitive reserve in a middle-aged cohort at risk for Alzheimer's disease. Arch Clin Neuropsychol 2015; 30:634–42.
[59] Lane AP, Windsor TD, Andel R, Luszcz MA. Is occupational complexity associated with cognitive performance or decline? Results from the Australian Longitudinal Study of Ageing. Gerontology 2017; 63:550–9.
[60] Smart EL, Gow AJ, Deary IJ. Occupational complexity and lifetime cognitive abilities. Neurology 2014;83:2285–91.
[61] Festini SB, McDonough IM, Park DC. The busier the better: greater busyness is associated with better cognition. Front Aging Neurosci 2016;8:98.
[62] Festini SB, McDonough IM, Park DC. Corrigendum: the busier the better: greater busyness is associated with better cognition. Front Aging Neurosci 2016;8:148.
[63] Fischer CE, Schweizer TA. How does speaking another language reduce the risk of dementia? Expert Rev Neurother 2014; 14:469–71.
[64] Perquin M, Vaillant M, Schuller AM, Pastore J, Dartigues JF, Lair ML, et al. Lifelong exposure to multilingualism: new evidence to support cognitive reserve hypothesis. PloS one 2013;8:e62030.
[65] Wan CY, Schlaug G. Music making as a tool for promoting brain plasticity across the life span. Neuroscientist 2010;16:566–77.
[66] Guure CB, Ibrahim NA, Adam MB, Said SM. Impact of physical activity on cognitive decline, dementia, and its subtypes: meta-analysis of prospective studies. Biomed Res Int 2017;2017:9016924.
[67] Stranahan AM, Martin B, Maudsley S. Anti-inflammatory effects of physical activity in relationship to improved cognitive status in humans and mouse models of Alzheimer's disease. Curr Alzheimer Res 2012;9:86–92.
[68] Larouche E, Hudon C, Goulet S. Potential benefits of mindfulness-based interventions in mild cognitive impairment and Alzheimer's disease: an interdisciplinary perspective. Behav Brain Res 2015;276:199–212.
[69] Zinsstag J. Convergence of EcoHealth and One Health. Ecohealth 2012;9:371–3.
[70] Ford AE, Graham H, White PC. Integrating human and ecosystem health through ecosystem services frameworks. Ecohealth 2015; 12:660–71.
[71] Leung Z, Middleton D, Morrison K. One Health and EcoHealth in Ontario: a qualitative study exploring how holistic and integrative approaches are shaping public health practice in Ontario. BMC Public Health 2012;12:358.
[72] Blanchet K. Thinking shift on health systems: from blueprint health programmes towards resilience of health systems Comment on "Constraints to applying systems thinking concepts in health systems: A regional perspective from surveying stakeholders in Eastern Mediterranean countries". Int J Health Policy Manag 2015;4:307–9.
[73] Dias R, Santos RL, Sousa MF, Nogueira MM, Torres B, Belfort T, et al. Resilience of caregivers of people with dementia: a systematic review of biological and psychosocial determinants. Trends Psychiatry Psychother 2015;37:12–9.
[74] Epstein RM, Krasner MS. Physician resilience: what it means, why it matters, and how to promote it. Acad Med 2013;88:301–3.