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A life-course and multifactorial approach to Alzheimer's disease: Implications for research, clinical assessment and intervention practices

Martial Van der Linden and Anne-Claude Juillerat Van der Linden
University of Geneva, Switzerland

Abstract
According to the dominant biomedical view, Alzheimer's disease (AD) has a precise, necessary and unifying neurobiological cause, which distinguishes it from other neurodegenerative diseases and normal ageing. However, different types of evidence specifically lead to questioning the foundations of this essentialist and category-based approach to AD. It seems more and more evident that AD represents a heterogeneous state, determined by multiple factors and mechanisms that interact and intervene throughout life. This other way of conceiving AD not only requires a change of research objectives, but also a profound modification of clinical assessment and intervention practices. It also appeals to follow the path of prevention.

Keywords
Alzheimer's disease, biomedical approach, assessment, intervention, prevention

Introduction

The predictions concerning the number of older people who, by 2050, will have cognitive impairment associated with impairments of daily living activities, namely persons with dementia, generate frequent alarmist announcements envisaging a tsunami of dementia cases. These cases are expected to submerge families and health care systems, and to impose on society an unbearable economic burden. In order to prevent this ''crisis of dementia'', the dominant biomedical position, which has gradually developed since about

Corresponding author:
Martial Van der Linden, Faculty of Psychology and Educational Sciences, University of Geneva, 40, Carl-Vogt Bvd, CH-1211 Genève 4, Switzerland.
Email: martial.vanderlinden@unige.ch

1970, considers it necessary to put more efforts into implementing the tools of the fundamental and clinical neurosciences to find the neurobiological cause of dementia, to develop neurobiological procedures to diagnose it as early as possible, and to identify pharmacological or other treatments to delay its onset and, ultimately, to cure it.

From this position, diagnostic categories (such as Mild Cognitive Impairment, MCI) were developed, corresponding to intermediate states between normal ageing and dementia. Historically, elderly persons showing mild memory or cognitive difficulties were considered to have benign age-related problems. However, a change of conceptualization occurred as a result of the biomedical approach toward ageing that led to the belief that these individuals had a disease, or at the very least, a condition likely to progress towards a dementing disorder.

In parallel, an increasing number of memory clinics were established, the main purpose of which was to identify people with a dementing disease or a pre-dementia state in order to administer pharmacological treatment. More recently, diagnostic procedures appeared whose purpose is to identify as early as possible, by means of biological markers, the presence of dementia even before it is expressed through cognitive deficits (*preclinical* or *asymptomatic* dementia). Thus, the reductionist biomedical approach to dementia has strengthened and, more generally, the medicalization and pathologization of brain and cognitive ageing have increased, along with the ensuing stigmatization.

Another approach to Alzheimer's disease and another research strategy

After the work of Alois Alzheimer in the early 20th century, the term Alzheimer's disease (AD) was initially reserved for the rare disease that mainly affected people in their fifties. Since the 1970s, however, the concept developed – first in the United States, and then more widely – that AD was a pandemic disease that could be identified, not on the basis of age, but on the basis of specific cognitive symptoms and neuropathological characteristics (namely neuritic plaques and neurofibrillary tangles). According to this view, AD has a precise, necessary and unifying neurobiological cause, which distinguishes it from other neurodegenerative diseases and normal ageing.

Different types of evidence specifically led to questioning the foundations of this essentialist and category-based approach to AD (a detailed description of these findings can be found in Van der Linden & Juillerat Van der Linden, 2014a; see also Lock, 2013). In particular, it has been shown that AD can express itself in different ways at the cognitive level. Scheltens et al. (2016) thus identified eight distinct cognitive sub-types in a large sample of patients diagnosed with AD dementia, and these cognitive clusters were associated with distinct demographical and neurobiological characteristics. In addition, the evolution of cognitive difficulties greatly varies from one AD person to another, and in many people (between 22% and 58%), the situation may remain stable or evolve very slowly for several years (up to 7 years), regardless of ''anti-Alzheimer'' medication (Bozoki, An, Bozoki, & Little, 2009; Mungas et al., 2010; Tschanz et al., 2011). Moreover, in a study that followed people with a diagnosis of AD and MCI for two years, Song et al. (2013) noted an improvement of cognitive functioning in some people and in parallel an improvement in brain damage, which suggests the dynamic nature of brain and cognitive ageing.

Furthermore, it has been increasingly recognized that co-occurrence of multiple pathologies (various extra- and intra-cellular abnormal protein deposits and other

pathologies, including cerebrovascular disorders and hippocampal sclerosis) is frequent in the brains of both cognitively intact and impaired aged persons (Dugger et al., 2014; Fotuhi, Hachinski, & Whitehouse, 2009; Jellinger & Attems, 2015; Wharton et al., 2011). Also, approximately 65% of people over 80 years old have amyloid positivity (revealed by neuroimaging; Rowe et al., 2010) and, according to the dominant biomedical position, could be diagnosed as having AD or pre-AD. In addition, in people over 85 years, the prevalence of Alzheimer-type pathology (amyloid plaques and neurofibrillary tangles) is similar, whether people have dementia or not (Mattsson et al., 2012).

Normal aging is also accompanied by changes in brain regions, in the same places where changes are observed, although more prominently, in people who have received a diagnosis of AD (Fjell, McEvoy, Holland, Dale, & Walhovd, 2014). More generally, as the extent of cognitive difficulties and brain changes varies considerably in normal elderly people, in those with MCI, and in those with AD (Mungas et al., 2010), it is impossible to precisely define the boundary between normal and abnormal cognitive, and cerebral aging. In this context, many studies have noted the low predictive validity of a diagnosis of MCI (for a review, see Stephan, Kurth, Matthews, Brayne, & Dufouil, 2010). In fact, individuals who have received this diagnosis (through various criteria and after controlling for age) do not predominantly progress to dementia (even at a long-term follow-up), but rather remain stable or return to normality, or their condition evolves into something that is not classifiable (Kaduszkiewicz et al., 2014; Marcos et al., 2016; Matthews et al., 2008; Mitchell & Shiri-Feshki, 2009; Ward, Tardiff, Dye, & Arrighi, 2013).

It must also be noted that, currently, there is no drug which has real effectiveness for the autonomy and quality of life of the people who have received a diagnosis of AD, or which can delay the development of this condition (Cooper et al., 2013). Even worse, Sona et al. (2012) showed, through a follow-up of 18 months, that the long-term use of cholinesterase inhibitors was associated with a higher risk of rapid cognitive decline in people with a diagnosis of AD. Of note is that cholinesterase inhibitors have also been associated with other adverse effects, in particular, a higher rate of bradycardia, syncope, insertion of a pacemaker, and hip fracture (Schneider, 2012). In addition, a meta-analysis and systematic review conducted by Tricco et al. (2013) showed that cholinesterase inhibitors and memantine did not improve cognitive abilities or functional status of individuals with MCI.

Finally, more and more epidemiological data show that the presence of cognitive difficulties in elderly persons is modulated by a variety of factors whose influence can occur at different stages of life. Included among these factors are physical activity and exercise, education and intellectual engagement level, social isolation, feeling of loneliness and social engagement, diet, stress and psychological distress, purpose in life, negative stereotypes concerning aging, vascular risk factors, diabetes, environmental toxins, head trauma, and smoking (see Blazer, Yaffe, & Liverman, 2015). Barnes and Yaffe (2011) estimated the effects that the reduction of seven risk factors (diabetes, hypertension in midlife, obesity in midlife, smoking, depression, low education level or cognitive inactivity, physical inactivity) would have on the prevalence of AD, by calculating the percentage of cases attributable to a given factor, and the number of cases that could be prevented by globally reducing risk factors either by 10% or by 25%. The authors estimate that a combined reduction by 10% of the seven risk factors would lead to a decrease of 1,100,000 AD cases worldwide and a 25% reduction of these factors would allow a decrease of 3,000,000 cases worldwide. This study thus shows how the lives of many older people

could be modified if effective prevention interventions were implemented (see infra). It should be noted that a plurality of risk factors has also been identified in persons with young-onset dementia, that is, dementia before 65 years of age (Nordström, Nordström, Eriksson, Wahlund, & Gustafson, 2013). Most of these factors could be traced at adolescence and could potentially be modifiable (such as use of neuroleptics, alcohol and other drug intoxication, high blood systolic blood pressure, depression).

All of these findings lead to the consideration that we must free ourselves from the outdated notion of AD as an essential disease with a necessary and unifying cause, and reinstate the different expressions of this supposedly specific disease in the broader context of brain and cognitive ageing, in its multiple problematic manifestations, under the influence of many factors intervening at all stages of life. According to Chételat (2013), we are entering a new era in which the unitary concept of AD as a disease characterized by a unique and specific pathological trajectory is gradually being replaced by a more complex vision that considers AD as a multifactorial pathological condition, subtended by several, partly independent, pathological processes that interact with each other according to different sequential organizations under the influence of various environmental and genetic risk factors, both common and specific. She therefore envisages the contribution of pathological mechanisms, other than those of tau and amyloid, in particular, vascular damage, neuroinflammation, abnormal connectivity, etc. More radically, Castellani and Perry (2012) argue that the scientific community let itself be seduced by neuropathological lesions (such as neuritic plaques, neurofibrillary tangles, or oxidative stress) and thus was unable to resist to temptation to believe that these lesions were the cause of AD. In doing so, researchers have confused cause and effect. Considering the total lack of progress in the implementation of curative treatments for this disease, as well as the lack of convincing evidence for the causal nature of these neuropathological changes, Castellani and Perry suggest that researchers and clinicians take more seriously the hypothesis that these changes constitute an adaptive mechanism or a protective response of the brain.

In an article entitled ''The Alzheimer Myth and Biomarker Research in Dementia'', Richard, Schmand, Eikelenboom, Westendorp, and Van Gool (2012) also considered that the exclusive focus on β-amyloid and tau pathological mechanisms as causal factors of AD led researchers to ignore the complexity and heterogeneity of dementia in elderly persons, and limited the development of new prevention and intervention strategies. They also indicate that most older people diagnosed with AD in fact present different types of brain damage (cerebrovascular disorders, alpha-synucleinopathies, hippocampal sclerosis, etc.), in addition to neuritic plaques and neurofibrillary tangles. In particular, they focus on the high frequency of cerebrovascular damage. In this context, reducing the risk of occurrence of cerebrovascular events (e.g. through rigorous treatment of hypertension) could contribute to delaying the installation of dementia and slowing the progression of cognitive decline. Finally, they consider it essential to take into account the timing of interventions targeting vascular risk factors. Indeed, the association between dementia and hypertension, obesity and high cholesterol, seems to depend on age, the risk of dementia being higher in the presence of these vascular risk factors when someone is in their fifties, but could attenuate and even reverse at the end of life. On the other hand, the association between diabetes and dementia seems more consistent, even during the last period of life.

Kling, Trojanowski, Wolk, Lee, and Arnold (2013) have called for a paradigm shift to explore the contribution of vascular problems to the onset of dementia. First, they propose giving up a taxonomic approach that distinguishes between different types of dementia

(e.g. AD, vascular dementia) and instead adopting an integrative approach by trying to understand the specific physiopathological mechanisms (and their interactions), at the cellular and molecular level, by which the various vascular, endocrinal, and metabolic risk factors, as well as endocrine and metabolic disorders (dyslipidaemia, hypertension, platelet/haemostatic/endothelial dysfunction, insulin resistance, inflammation, stress), contribute to the phenotypes of dementia and their neuropathological expressions. Moreover, given the important interactions between the systems involved in vascular and metabolic dysfunctions, these researchers suggest adopting a systemic perspective, which will lead to the development of dynamic and interactive models of the processes involved in the progression of cognitive decline in elderly persons.

More generally, Brayne and Davis (2012) consider that the conception according to which the physiopathological processes of AD are clearly different from those involved in ageing is most questionable. This conception results from the tendency to reify diagnostic entities (i.e., to consider them as concrete and stable entities) and to offer simplistic postulates concerning etiological factors, as well as to the fact that few longitudinal studies have been conducted on representative samples of the real population (most studies focused on volunteers, on people recruited in memory clinics, and on persons under the age of 85 years, which considerably limits the generalization of the results). Thus, Brayne and Davis plead for the implementation of a dementia research more rooted in the real population.

In the same vein, in an article entitled "Scientific Truth or False Hope? Understanding Alzheimer's Disease from the Perspective of Aging", Chen, Maleski, and Sawmiller (2011) proposed a model in which the root of dementia is the increase in life expectancy. In other words, in their model, natural ageing would play an important role in the neurodegenerative phenomena, which would thus form an integral part of the body modifications that occur in the last stage of life. Moreover, the fact that not all elderly people present dementia points not to a pathogenic agent, but to different risk factors: in advanced age, the fragility of brain cells makes them vulnerable to any sort of negative influence, such as lack of physical and cognitive activity, inadequate nutrition, or social isolation. By acting in an additive way, and during the final stages of extended longevity, these risk factors would trigger cell death or amplify the negative effects of neurodegenerative natural phenomena. Because of the variability of life contexts, the action of these risk factors would have an essentially probabilistic nature. The authors add that other problems may affect the ageing brain and contribute to its problematic evolution, in particular vascular and infectious problems, the effects of head trauma, or genetic mutations. Thus, they consider AD to be a heterogeneous condition under the influence of various risk factors and related to advanced age. In this context, interventions should not aim to inhibit pathogenic processes, but, rather, should target risk factors (prevention) and protect old neurons. According to Chen et al., such an approach will lead to substantial progress only if general awareness develops, leading to funding priorities. In this regard, they indicate how scientific research in the field of ageing is subject to significant social pressure: Fear has infiltrated scientific research, pushing researchers to find a cure, to the detriment of scientific truth.

Herrup (2010) also considers the more important risk factor in the development of the condition called AD to be age, with its inherent reduction in the structural complexity of brain cells and defences. Starting from a brain naturally weakened by age, three key events lead to dementia: (1) Initiating brain damage occurs, that is related to various problems such as physical trauma, disease, or important infection, vascular problems, metabolic stress, or

stress associated with a major life event; (2) This damage causes a chronic inflammatory process that adds additional and constant stress to brain cells already weakened by age; (3) Dementia follows a significant change in the physiology of the brain cells that leads to major synaptic dysfunction and neuronal death. In the younger persons, and in the absence of predisposing factors (including genetic factors), brain damage caused by initiating events is corrected by a natural brain response that has been developed for this purpose (including the production of β-amyloid, which accumulates naturally with age). On the other hand, advancing age leads to a higher frequency of brain damage and, along with this, a prolonged response to correcting the damage. And it is precisely this persistent response (not the initiating brain damage) that generates different phenomena leading to dementia, such as a cycle of β-amyloid deposition (which stimulates the immune response, which in itself stimulates further production of β-amyloid), attempts at cell cycle reentry, synaptic dysfunction, and, ultimately, neuronal death. According to Herrup, the presence of amyloid plaques, although correlated with problematic brain ageing, is not an essential component of the lead-up to dementia: in other words, the accumulation of amyloid plaques is regarded as a mechanism that is distinct from the three mandatory steps leading to dementia. Lastly, the author also states that different types of initiating damage in a brain weakened by age will lead to different responses of the brain cells and thus to different problematic manifestations. In addition, various types of brain damage can coexist (and thus also various brain responses), which lead to the co-occurrence of different types of problematic manifestations (corresponding to what is conventionally called mixed dementia, which is particularly common).

Overall, these conceptions suggest that AD should be reinstated within the more general framework of brain and cognitive ageing by taking into account the multiplicity and the probabilistic nature of the factors that modulate the evolution of this ''disease''. Research in keeping with these approaches should therefore consider the brain and cognitive ageing in terms of a continuum, rather than on the basis of disease categories (Walhovd, Fjell, & Epseseth, 2014). Such studies should also attempt to identify more precisely the different factors (biological, medical, psychological, social, environmental), and their inter-relationships, in the more or less rapid and progressive development of deficits affecting some cognitive domains, deficits that vary among individuals. At the neurobiological level, it is necessary to break away from the reductionist approach, which is based on the exploration of small molecules, in order to examine other hypotheses, in particular those that suggest interactions between various combinations of neurobiological mechanisms. The biomarkers should thus be considered as the expression of certain general mechanisms – within a complex set of interacting mechanisms – that may be present to different degrees and in different combinations in elderly people with varying cognitive difficulties. Furthermore, rather than trying to locate the brain regions specifically affected in AD or in other types of dementia, it would be more appropriate to explore the factors that contribute, with advancing age, to the progressive reduction in coordination (integration) of brain activity within and between different large-scale brain networks (Ahmed et al., in press; Andrews-Hanna et al., 2007). In this context, Walhovd et al. (2014) suggested that the considerable potential of neuroplasticity which characterizes the brain's default network makes it particularly vulnerable to various (environmental and internal) factors likely to generate cognitive decline (see also Neill, 2012). Other high-level networks could, however, also be the starting point of problematic cerebral ageing resulting from neuropathological changes and psychological dysfunctions of a different nature. From this point of view, it would be

particularly interesting to examine the extent to which a developmental fragility of certain brain networks exists in some elderly people, which could explain, in interaction with other actors (biological, psychological, social, and environmental), the presence of disproportionate and progressive deficits in certain cognitive domains. Miller et al. (2013; see also Seifan et al., 2015) thus showed that developmental difficulties of language acquisition lead, in the elderly, to an earlier, higher, and more isolated prevalence of progressive phonological language deficits, associated with posterior temporo-parietal atrophy (the logopenic variant of primary progressive aphasia).

Further exploration also necessitates taking into account the compensatory capacities (the brain and cognitive plasticity) of the elderly and examining the factors that modulate this plasticity and thus contribute to interindividual differences. According to the scaffolding theory of aging and cognition (STAC; Park & Reuter-Lorenz, 2009), individual differences in level of cognitive functioning in older adults can be understood in terms of combined effects of adverse and compensatory (''scaffolding'') neural processes. Scaffolding is considered as the recruitment of additional circuitry that strengthens declining brain function. A revised version of this theory (STAC-r; Reuter-Lorenz & Park, 2014) incorporate life-courses factors (see supra) that operate to either enhance or deplete neural resource and also influence compensatory processes. As mentioned by Reuter-Lorenz and Park, an important challenge is ''to understand how strongly different extrinsic factors modify trajectories of aging, the developmental time course of such influences, and relatedly how much plasticity exists in the aging brain at different stages of the life course'' (p. 364).

Such a perspective, taking into account the variability and complexity of cerebral and cognitive aging, leads to envisaging the assessment of cognitive and functional difficulties differently in the elderly, by integrating the multitude of contributing factors, rather than by imprisoning the person in pathologizing and stigmatizing diagnostic categories. A rebalancing of the interventions in favour of individualized psychosocial approaches is also necessary in order to improve quality of life, everyday life functioning, stress management, self-esteem, and sense of personal continuity, along with prevention, the objective of which is to delay or reduce the problematic expressions of brain and cognitive ageing.

A modification of neuropsychological assessment and intervention practices

Another way of conceiving the brain and cognitive ageing, by taking into account the variety of factors that modulate its more or less problematic evolution, should lead to significant changes in neuropsychological assessment (see Van der Linden & Juillerat Van der Linden, 2014b). Indeed, the heterogeneity and multifactorial character of cognitive and socio-emotional manifestations of the so-called neurodegenerative diseases and the important overlap between them generally render irrelevant the use of neuropsychological examination for differential diagnosis (i.e., to identify the distinctive cognitive characteristics of these ''diseases'') or in a predictive function (i.e., to predict the evolution of cognitive difficulties). However, the neuropsychological assessment will always aim to identify the emergence of cognitive, socio-emotional and functional difficulties in the elderly, and to understand their nature and monitor their evolution. Besides, this different conception of problematic brain and cognitive ageing should lead to greater emphasis on

individualized psychological and social interventions, in order to optimize the quality of life and well-being of the elderly, as well as to prevention interventions aimed at delaying the problematic aspects of ageing or minimizing its effects. In this context, other aspects of neuropsychological assessment will be critical: (a) to explore the experiences of older people (and their families) having difficulties; (b) to understand the nature of problems in everyday life in order to propose psychosocial interventions; (c) to identify risk factors that could be the object to preventive measures (see infra). This assessment should be based on the perspective of the elderly persons themselves and not just on that of their relatives or caregivers. Indeed, it was found that people with a diagnosis of mild or moderate dementia were able to provide a valid report of their well-being, their quality of life and the quality of care provided to them (Beer et al., 2010; Mak, 2011).

More generally, this evaluation process should favour the formulation of an individualized and integrative psychological interpretation (a case formulation), taking into account different types of psychological processes, and also leading to the identification of the possible role of social factors, as well as life events and biological factors. This could be seen in the context of the ''mediating psychological processes'' model, addressing the complex and interconnected nature of the psychosocial problems (Kinderman, 2005, 2014). This model proposes that biological and social factors, together with the person's individual experiences (life events), lead to psychological problems through their conjoint effects in influencing or disrupting relevant psychological processes. It is important to stress that disruption of psychological processes is not limited to cognitive processes, but that motivational, emotional, inter-personal and identity processes can also be involved. In addition, Kinderman (2015) suggests that, rather than using diagnostic labels for putative disorders (such as AD or dementia), we should instead make a list of a person's problems. Furthermore, in order to understand these well-defined and specific problems, we should develop an individualized psychosocial formulation detailing the hypothesized disruption of psychological processes or mechanisms. It seems to us that this model has obvious implications for clinical assessment in elderly presenting with cognitive, socio-emotional and functional difficulties.

Also of importance is conceiving a different way to announce the results of a neuropsychological assessment and, more generally, of a clinical exploration: an announcement that does not confine the elderly presenting cognitive and functional impairments in ''end of life diseases''. Rather, it is necessary to emphasize what connects the person to the others and to focus on his or her preserved abilities. More specifically, this announcement process must consist in informing the elderly person that he or she actually has difficulties in certain domains, that ageing inevitably comes along with this type of difficulties, even if there are differences between the individuals in the importance of these difficulties – partly due to differences in life courses and concomitant health problems –, and also that, if he or she has more difficulties than other elderly in certain domains, there are also preserved abilities. In addition, the person has to be informed that the evolution of these difficulties is not predictable, that there are large inter-individual differences in this evolution and that both the difficulties and their evolution are determined by various factors. It should also be stated that one can still live well with cognitive difficulties, and have vitality, meaning in life and a role in society. The person should also be told that there are different actions susceptible to attenuate the impact of the cognitive and functional difficulties, and to slow down their evolution, including remaining involved in society, within one's means, and that adapted psychosocial interventions can help to have a better quality of life and well-being.

In terms of intervention, we consider that no "turn-key" intervention program is able to meet the different objectives of a psychological approach to the difficulties of an elderly person. Rather, it is necessary to adopt an individualized approach, targeting specific goals in everyday life (established with the person and her or his relatives), and based on different types of psychological processes and interventions. This approach should be multiple and integrated. At present, few studies have shown the beneficial effects of an individualized intervention program in persons with dementia: we can nevertheless mention the simple blind, randomized study of Clare et al. (2010), which demonstrated the clinical efficiency of a personalized cognitive revalidation. In parallel to these individualized psychological interventions, it is also necessary to promote the commitment of elderly persons with dementia to activities within the community and which can help to strengthen physical condition, sense of control, identity, personal continuity and purpose in life, openness to society, as well as intergenerational relationships.

Following the path of prevention

The data accumulate to support the view that the risk of dementia in the elderly is determined by multiple factors (encountered at different stages of life and whose effect largely depends on age) and to appeal to follow the path of prevention, by implementing multiple interventions throughout life (e.g. increasing educational level in children and young adults, actively controlling vascular risk factors in adulthood, maintaining an socially, physically and mentally active life during midlife and old age, etc.). The importance of prevention has been clearly defended by Barnett, Hachinski, and Blackwell (2013) in an article eloquently entitled "Cognitive health begins at conception: addressing dementia as a lifelong and preventable condition". The authors remind that half the risk of AD is explained by seven risk factors: diabetes, hypertension, obesity, smoking, depression, cognitive activity/education and physical activity (see also Barnes & Yaffe, 2011; Deckers et al., 2015). In addition, the evidences are particularly compelling for a group of metabolic factors (hypertension, diabetes, obesity, and serum lipids) present during midlife (forty and fifty years old). They also mention that the risk of dementia presumably begins from birth, or even before (in the mother's womb), through factors acting on the brain and cognitive development, such as the neonatal environment (diet, exposure to toxins, maternal smoking), social insecurity, etc. In this context, recent studies have reported the existence of a lower prevalence and incidence of dementia in people who were born in the second quarter of the 20th century, compared to those who were born in the first quarter (Larson, Yaffe, & Langa, 2013) and a decline of the incidence of dementia over the course of three decades (Satizabal et al., 2016). This decrease was interpreted as reflecting an increase in education level and a better prevention of vascular diseases.

In consideration of the reservations expressed by some researchers regarding the interest of prevention, Friedland and Nandi (2013) discuss how the absence of definitive evidence concerning the efficiency of dementia prevention should not hinder the implementation of preventive measures based on existing data. These authors demonstrate the unrealistic nature of any "definitive" study" about the interactions between lifestyle and cognitive health in older people and they consider it is time to admit that such a study cannot be performed. Moreover, as noted by Power (2010), we must not fall into paranoia and start to obsessively dissect our existence in order to identify the multiple factors (related to our previous life experiences, our social network, our lifestyle, what we eat, what we drink,

etc.) that could be associated with the development of problematic brain and cognitive ageing. It does nevertheless seem possible to reduce or delay the most problematic manifestations of cerebral ageing by reducing vascular risk factors, eating more healthily, exercising, engaging in stimulating activities and having goals in life. However, becoming obsessed with every single thing we do, eat or drink will not reduce more the risk of cognitive problems than maintaining a ''healthy moderation''.

More generally, the idea that a ''successful aging'' (Rowe & Kahn, 1998) could be achieved by adopting an appropriate lifestyle leads to devalue the elderly with cognitive and functional disorders. Similarly, should we then consider that the people who have shown developmental or congenital disabilities are doomed from the beginning of their lives to a ''failed aging''? Thus, keep in mind that many of us will encounter physical, cognitive and functional difficulties while ageing. This will not make us persons of lesser value. Brayne, Gao, Dewey, Matthews, and Medical Research Council Cognitive Function and Aging Study Investigators (2006) thus showed that, even if preventive measures are likely to reduce the risk of dementia at a given age (i.e., extending life expectancy in good cognitive health), this reduction will lead to a further extension of life, and therefore the cumulative risk of developing significant cognitive difficulties will remain high (with 30–40% of dementia occurring at 90 years old), even in populations with a lower dementia risk at certain ages. In other words, the ageing of the population will lead to an increase in the number of elderly people who will die with important cognitive disorders, even in the presence of prevention programs. In addition, the conception of successful aging, which focuses on individual choice of a potentially beneficial lifestyle and on personal responsibility in optimizing aging, ignores the fact that these choices and responsibilities are strongly constrained by socio-economic and environmental factors (financial resources, access to health care, stimulating activities, etc.; Katz & Calasanti, 2015).

A novel and pragmatic model for prevention trials has been provided by the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability study (FINGER; Ngandu et al., 2015), a long-term and large randomized controlled trial aimed to assess the protective effects of a multidomain intervention (comprising dietary advice, an exercise programme, social activities, cognitive training, and management of metabolic and vascular risk factors) on cognition in at-risk elderly people from the general population. At the end of the two-year follow-up period, findings showed significant intervention effects on global cognition, executive functioning and processing speed, as well as effects on body mass index, dietary habits and physical activity. There were also beneficial effects on risk of cognitive decline. A seven-year extended follow-up will be done to assess intervention effects on incidence of dementia and associated functional outcomes.

Conclusion

In an article published in parallel in the *Journal of Alzheimer's Disease* and the *Journal of Intergenerational Relationships* (in order to establish a bridge between the two readerships), Whitehouse (2013a, 2013b) returns to the limitations of the dominant biomedical approach to AD and calls for an integrative approach to what he termed ''age-related cognitive challenges''. This integrative approach would restore the balance between the biomedical point of view (assuming the complexity of the biological mechanisms involved in ageing) and the psychological, social, environmental and cultural perspectives. It should particularly focus not only on intergenerational relations and the development of new educational

structures (promoting learning throughout life: learning through community service, civic spirit, and involvement of the elderly), but also on social, environmental, and public health actions, allowing a reduction in modifiable risk factors for the problematic brain and cognitive ageing. This conception also invites us to reflect on ourselves and to have more humility regarding the age-related challenges we will face in the future. It should lead us to consider the world not as divided between those who have AD and those who do not, but rather as a place where we all share the vulnerabilities of brain and cognitive ageing. In addition, it could help to create more unity between generations, and to develop social structures in which the elderly, regardless of their problems, may find goals and meaningful roles in society, as well as individualized support to maintain their autonomy and well-being. In other words, dementia should be considered as a life experience, which can lead to changes in the perception that the person has of the world, but in which learning and personal development remain possible (Power, 2010).

As a consequence, actions should be taken at a social and political level (in different domains: living environments, social structures, social and health policy) to promote social engagement of older people, and interpersonal (and more particularly intergenerational) relationships, to facilitate access to prevention and support resources, and to reduce poverty. The implementation of such measures requires the development of interventions and structures in local communities in direct connection with community services, associations, family doctors, and so forth.

An example of such structures can be found in various countries, in so-called ''Dementia-friendly communities'', but it is usually restricted to a couple of local uncoordinated projects. In Switzerland, a full program named VIVA (www.association-viva.org; in French, the acronym means ''Valorizing and Integrating for a Better Aging''), subsidized by the local authorities, has been developed within a Geneva's suburb. It is run by psychologists and its activities are organized around a few domains known for enhancing cognitive functioning, and psychological well-being. These activities are adapted to welcome both elderly people living within the area, and people facing dementing disorders, thus playing a role both at the prevention and integration levels. Several activities, particularly intergenerational ones, have taken place in long-term residential homes.

- Stimulating physical, cognitive and social activities: Qi Gong classes, open-air gym programmes, computer classes, participation to didactic presentations of contemporary art exhibitions, group of poetry, weekly ''café'' and Sunday brunches, etc.
- Intergenerational activities, mostly shared with local schools or after-school: mentorship for reading, gardening, painting, discovery of the area's historical and natural environment, knitting and crochet work, rap music singing, etc.
- Thematic meetings (''I am getting old and I am doing well'') and workshops around health-related questions raised by the elderly (such as improving sleep, eating habits, memory, preventing falls, etc.), organized with a nearby health house.

As a result, many elderly people taking part to this program describe an improvement in their sense of purpose, in their sense of belonging to the community, as well as an increased openness to other people; significant changes have also been observed in the way that children consider elderly people, as they move from holding a view that reflect underlying ageism (wrinkles, hearing problems, loss of autonomy, etc.) to acknowledging the value of experience and shared friendship after the intergenerational activities. Such an experience at

the level of a community indicates how changes could be obtained, mainly through a bottom-up process, though supported by local politics.

The development of another approach to brain and cognitive ageing, taking into account elderly persons in all their complexity and individuality, will require the thwarting of multiple cultural and ideological strengths (profoundly anchored in the myth of eternal youth), but also the power of what Whitehouse and George (2008) call the ''Alzheimer Empire'', in its medical, scientific, political, industrial and associative components.

More generally, a change in conception of cerebral and cognitive ageing also involves a profound modification of the perception that elderly persons with cognitive difficulties have of themselves and that others (the society) have of them. In fact, the question of the social regard given to dementia, under the influence of the dominant biomedical model, refers to the more general question of the role given to vulnerable citizens in our society. According to Zeilig (2013), dementia can be considered as an image of our society (a cultural metaphor), ''revealing what we really are''. It leads us to consider the similarities between the way we live (in a ''demented'' society) and how the person who has received a diagnosis of dementia – but also any other vulnerable (young or old) person – is trying to become integrated in this world: a world that values efficiency, individualism, and the incessant acquisition of cognitive skills at the expense of compassion, solidarity, social commitment, and the ''memory of our shared humanity''. Dementia is a prism through which we can more clearly see the state of our society and the need to change it. Thus, to defend a different way of thinking about ageing is also to defend another type of society in which vulnerability, difference, and finitude have all their place.

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Author Biographies

Martial Van der Linden, PhD, is professor of Psychopathology and Neuropsychology at the University of Geneva. His research aims at better understanding cognitive and socio-emotional dysfunctions in people suffering from brain lesions or presenting psychopathological symptoms. A part of his work is also dedicated to the effects of aging on daily life, in a multifactorial and integrative approach.

Anne-Claude Juillerat Van der Linden, PhD, is a clinical psychologist specialized in neuropsychology; she has created a psychological counselling service for elderly people facing age-associated psychological difficulties, and is also a lecturer at the University of Geneva. She and Martial Van der Linden have founded in 2009 an association entitled VIVA, French acronym for ''Valorizing and Integrating for a Better Aging'', in order to help people age well within a local community.