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A life-span and plurifactorial view of Alzheimer's disease

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ABSTRACT

The dominant biomedical position considers Alzheimer's disease (AD) to be intrinsically different from normal ageing and other neurodegenerative diseases and proposes that, by pursuing extensive research on what are considered the specific neuropathological characteristics of AD (i.e., neurotic plaques and neurofibrillary tangles), we will eventually be able to identify the cause of this disease and develop medical treatments that will allow us to successfully cure it. However, results of numerous recent studies go against this essentialist and category-based view and instead suggest that the cognitive, emotional, behavioural, and functional difficulties that some people experience as they grow older are modulated by a myriad of factors and mechanisms that interact throughout the lifespan. Importantly, this alternative way of conceptualising Alzheimer's disease implies a shift of focus in terms of research objectives and calls for significant changes in terms of neuropsychological assessment and intervention in clinical practice.

Introduction

Numerous studies predict that the number of older adults who have cognitive impairment associated with impairments in the realisation of activities of daily living, namely people with dementia, will triple by 2050[1] and that this increase will submerge families and healthcare systems, as well as impose an unbearable economic burden on society. In order to prevent this so-called "social crisis of dementia", the dominant biomedical position considers that we should strive to find the neurobiological causes of dementia, develop neurobiological procedures to diagnose it as early as possible, and identify pharmacological treatments to delay its onset and, ultimately, to cure it.

From this position and in line with these objectives, significant changes in clinical practice have been implemented since the early 1990s[2]. First, an increasing number of memory clinics have been established in order to identify people with a dementing disease, or with a pre-dementia state, and to provide them with (so far non-effective) pharmacological treatments. Second, diagnostic categories such as Mild Cognitive Impairment (MCI[3]) were created to account for the cognitive difficulties, formerly considered to be benign and related to ageing, that some elderly people experience as they grow older. Finally, new diagnostic procedures based on biological markers were developed in order to identify the presence of dementia as early as possible (i.e., even before it is expressed through cognitive deficits).

Altogether, these changes in clinical practice indicate that the reductionist biomedical approach to dementia has strengthened

throughout the last 30 years and that, consequently, medicalisation, pathologisation, and stigmatisation of cerebral and cognitive ageing have increased.

Limits of the dominant biomedical approach to Alzheimer's disease

According to the dominant biomedical position, Alzheimer's disease (AD) is a chronic and progressive disease that can be identified on the basis of specific cognitive symptoms (in particular, episodic memory deficits) and neuropathological characteristics (i. e., neurotic plaques and neurofibrillary tangles)[4]. Importantly, this approach considers AD to be intrinsically different from normal ageing and other neurodegenerative diseases and proposes that, by pursuing extensive research on what are considered the specific neuropathological characteristics of AD, we will eventually be able to identify the cause of this disease and develop medical treatments that will allow us to successfully cure it.

However, throughout the last two decades, different types of evidence led a growing number of scientists to question and criticise the foundations of this essentialist and category-based approach[5-8] (see Van der Linden[9] for a complete review). In particular, several studies have highlighted that AD can express itself through different cognitive deficits. For instance, using latent class analysis, Scheltens and colleagues[10] have identified eight distinct cognitive profiles in a large sample of patients diagnosed with AD. Amongst these profiles, only two were characterised by predominant memory impairments, while the other six described a mixture of language, attentional, executive, and/or visuospatial difficulties without memory impairments. Importantly, all of these profiles were associated with different demographical and neurobiological characteristics. Taken together, these results suggest that AD does not have any diagnostic specificity at the cognitive and biological levels and further imply that the current biomedical conceptualisation of AD cannot account for the complexity and heterogeneity of this condition.

In the same vein, numerous studies have demonstrated that the evolution of cognitive and functional difficulties can greatly vary amongst people diagnosed with AD. For instance, Tschanz and colleagues[11] have shown that the deterioration rate of older adults with dementia commonly differs from one person to another and that, for a significant proportion of people with this condition, the progression of their cognitive, behavioural, and functional difficulties is slow, or even null, throughout their last years of life. Furthermore, other studies[12] have found that spontaneous improvement can be seen in both brain structure and cognitive function amongst some older adults who were diagnosed with AD and cases of "reversible" AD have also been described[13]. Importantly, all of these studies suggest that age-related brain modifications are the results of a dynamic process that involves many risk and protective factors.

In this context, it is also worth noting that many authors have criticised the use of MCI in clinical practice because of the low validity of this diagnosis[14]. Specifically, Klekociuk and colleagues[15] have pointed out that the criteria for MCI have not been clearly operationalised and have also emphasised that MCI is longitudinally unstable, with many people who bear this diagnosis remaining stable or "recovering" to age-appropriate levels of functioning later in their life.

Finally, at the cerebral level, it is now well recognised that co-occurrence of multiple pathologies (e.g., various extra- and intra-cellular abnormal protein deposits, cerebrovascular disorders, hippocampal sclerosis, etc.) is frequent in the brains of both cognitively intact and cognitively impaired older adults[16-18]. Importantly, this finding implies that it is impossible to define a clear boundary between normal and abnormal ageing at the cerebral level.

A life-span plurifactorial view of Alzheimer's disease

Altogether, these findings have lead a growing number of authors to suggest that we must free ourselves from the reductionist biomedical conceptualisation of AD and that, instead of imprisoning people in pathologising and stigmatising diagnostic categories, we should reinstate the different expressions of this supposedly specific disease in a broader framework of cerebral and cognitive ageing (see Van der Linden[19] for a detailed presentation of this perspective).

Explicitly, according to this alternative and more recent perspective, the nature and extent of the cognitive and functional difficulties that people experience as they grow older are modulated by a myriad of factors and mechanisms that interact throughout the lifespan[20-22]. In particular, numerous epidemiological studies have shown that the factors that influence cognitive and cerebral ageing are biological (e.g., age, cardiovascular risk factors, diabetes, etc.), psychological (e.g., depression, anxiety, stress, etc.), environmental (e.g., environmental toxins, etc.), social (e.g., social isolation, etc.), cultural (e.g., living in a society that holds negative stereotypes towards ageing), and related to one's lifestyle (e.g., lack of regular physical activity, etc.) in nature[23]. Importantly, these factors are thought to operate through a complex set of interacting mechanisms[24] and to function either as risk or as protective factors depending on how each person relates to them individually.

To date, only a few authors have tried to adopt an ageing perspective in view of understanding how the mechanisms that are implicated in the development of cognitive and functional difficulties in late life operate. One notable contribution to this line of thought is Herrup's theory[25],

which proposes that there are three key steps to the development of AD: (1) an initiating brain damage that can be related to various types of problems (e.g., physical traumas, vascular problems, stress associated with a major life event, etc.), (2) a prolonged neuroinflammatory response, and (3) a discontinuous cellular change-of-state involving most types of brain cells. Explicitly, Herrup explains that advancing age leads to a higher frequency of brain damage and that, because getting older naturally diminishes the structural complexity of brain cells and weakens the brain's defences, any form of brain damage that occurs in old age will lead to a prolonged neuroinflammatory response in an attempt to correct the damage. According to this theory, it is the prolonged nature of this neuroinflammatory response that generates the different neurobiological phenomena that can lead to AD (i.e., amyloid deposition cycle, attempts at cell cycle re-entry, synaptic dysfunction, and, ultimately, neuronal death). Importantly, Herrup considers that different types of initiating damage can co-exist and that each type of damage will generate different responses from brain cells, which will in turn lead to different types of problematic manifestations.

Implications for research and clinical practice

Adopting a perspective that takes into account the variability and complexity of cerebral and cognitive ageing calls for a shift in terms of research objectives and leads to envisaging significant changes with regards to neuropsychological assessment and intervention in clinical practice[26] (see Van der Linden[19] for a more detailed presentation). Explicitly, in terms of research, it now seems essential that more studies be conducted from a perspective that considers cerebral and cognitive ageing as a continuum rather than on a categorical basis[27]. In addition, rather than solely focusing on small molecules, researchers should adopt an integrative and systemic perspective[24] and aim to examine how various combinations of adverse and compensatory neurobiological mechanisms contribute to the development of the different phenotypes and neuropathological expressions observed in dementia[28].

In terms of assessment practices, taking into consideration the heterogeneity and multifactorial character of the cognitive, behavioural, and socio-emotional manifestations of the so-called neurodegenerative diseases renders irrelevant the use of neuropsychological assessments for differential diagnosis, or for predicting the evolution of cognitive difficulties. Instead, we believe that the objectives of a neuropsychological assessment should remain to identify the emergence of cognitive, behavioural, socio-emotional, and functional difficulties in the elderly, to understand the nature of these difficulties, and to monitor their evolution. Importantly, we also argue that clinical neuropsychologists should (a) explore how the person (and his or her family/carers) experiences his or her difficulties, (b) identify risk factors that could be the object of preventive measures, and (c) aim to understand the nature of the person's problems *in everyday life,* so as to more efficiently optimise the quality of life and well-being of older adults by means of individualised psychological and social interventions. More generally, we think that clinicians should conduct their neuropsychological assessment with the aim of formulating an individualised and comprehensive case formulation[29].

Finally, with regards to intervention practices, due to the heterogeneity and complexity of cerebral and cognitive ageing, it seems unlikely that any "ready-made" intervention program will be able to meet all of the different needs of elderly adults who experience cognitive and/or functional difficulties. In particular, research has shown that, to date, there exists no pharmacological intervention that has been shown to have a real positive effect on the autonomy and quality of life of people diagnosed with this condition[30]. In order to promote older people's wellbeing and autonomy, we therefore suggest that clinicians should adopt an individualised and multifaceted approach in their practice, and that they should target specific goals (established with the person and with her relatives) that can have a concrete impact on people's daily life (see Clare[31] and Jha[32] for illustrations of this principle). Furthermore, in view of the variety of factors that can influence cerebral and cognitive ageing throughout the lifespan, we also believe that preventive measures have a significant role to play in terms of future interventions. In support of this claim, Barnes and Yaffe[33] have recently estimated that the reduction of seven risk factors (i.e., depression, smoking, diabetes, hypertension in midlife, obesity in midlife, low education level or cognitive inactivity and lack of physical activity) would lead to a significant decrease in the number of AD cases worldwide. Importantly, the results of this study imply that we could significantly change ageing trajectories by implementing a series of preventive measures on a societal level (e.g., early detection and management of cardio-vascular diseases and diabetes, encouraging people to exercise regularly and to maintain a socially and cognitively active life throughout their midlife and old age, etc.), but they do not intend to convey the message that people should be held responsible for their cognitive and functional difficulties if they experience some in later life[34].

Conclusion

In light of this short review, we would like to conclude by emphasising that adopting this lifespan and plurifactorial perspective on AD and dementia invites us to think differently about ageing. In particular, it leads us to consider the world as a place in which we all share vulnerabilities of cerebral and cognitive ageing and, instead of simply separating those who present cognitive and functional difficulties from those who do not by means of a diagnosis,

it encourages us to create more unity between generations.

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Declaration of competing interests

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