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Cognitive Functions and Neurotropic Factors Associated with Aging: A Review

ABSTRACT

RESEARCH OBJECTIVE: The aim of the present article was to make a narrative review about the relation of cognitive functions and neurotrophic factors with aging.

THE RESEARCH PROBLEM AND METHODS: The research problem concerns the issue of aging and the changes in cognitive and biochemical functioning that may occur in this process. The article uses the method of critical analyzes as well as the analyzes of the reference literature.

THE PROCESS OF ARGUMENTATION: The first section of the article discusses population aging, the second addresses changes related to cognitive functions during aging. The third part show biochemical aspects that can directly influence the cognitive functions already mentioned, and on aging in general.

RESEARCH RESULTS: The result of this review points out that the world population is aging in an accelerated way and during this process of aging there are several changes in the organism of the elderly, among which stand out the cognitive and biochemical, one being directly related to the other. In this case, there is a relation of the neurotrophic factors, which may be responsible for the changes in cognitive functions, specifically spatial memory alterations.

CONCLUSIONS, INNOVATIONS AND RECOMMENDATIONS: It is necessary that more studies be carried out with this population, which may trace the elderly with cognitive impairment that may be suggestive or conclusive of

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a neurodegenerative disease. In addition, biochemical data may contribute to the search for new therapeutic models or early identification for Alzheimer's disease or other associated dementias.

→ **KEYWORDS:** **AGING, COGNITIVE IMPAIRMENT, NEUROTROPHIC FACTORS**

The world's aging population

Population aging is directly related to both declining fertility and birth rates, as well as to efforts aimed at improving the population's living conditions. According to data from the Institute of Geography and Statistics (IBGE) (2010), the percentage of the population that is reaching old age is growing and occupying an ever larger space in our society. However, in recent years a change has been taking place worldwide. It is forecast that by the year 2025, there will be around 35 million elderly in Brazil, with our country occupying 6th place in regards to the total number of elderly in the population.

Considering the increase in the number of elderly within the population, it is worth highlighting the so-called "older, oldest old or elderly in advanced age" (above 80 years), which have been growing disproportionately, becoming the fastest growing segment of the population in recent years, and now accounting for more than 12% of the elderly (Oms & Opas, 1998; IBGE, 2010). Thus, this sub-group is altering the age composition within the age group itself, that is, the elderly population is also aging, generating a heterogeneity within the population segment called "the elderly" (Camarano, 2002). Older people aged 80 years or more account for about 1.1% of the elderly population in Brazil (Brazil, 2006).

Aging can be considered a process that affects the body's major systems and produces a progressive loss of function (Santos, Andrade, & Bueno, 2009; López-Otín et al., 2013). Elderly people are more prone to mental and neurological dysfunctions, such as alterations in cognitive function, memory, attention, language, praxia, visuoconstructive ability and executive function, as well as being prone to depression and depressive mood disorders (Mattos & Paixão Junior, 2010). The cognitive processes mediated by the hippocampus and prefrontal cortex are the most vulnerable to the aging process (Barrientos et al., 2015). Both regions are prone to synaptic changes that may be directly related to the decline in cognitive performance seen during aging (Morrison & Baxter,

2012). Although memory deficit is an important factor which causes functional impairment in daily life, other symptoms are also reported, such as attention deficits related to naming, reasoning and visuospatial skills (Mesulam, 2009).

Aging and cognition

With the global population constantly aging, the study of cognitive impairment has received a great deal of attention, as it is one of the main areas affecting public health and generating social problems (Brayne, 2007). Cognition is essential for functional independence, living independently, managing finances, taking medications properly, and driving safely. In addition, intact cognition is vital for humans, as it enables effective communication including the processing and integration of sensory information, and being able to provide the appropriate response to a given situation (Murmam, 2015).

Therefore, cognitive abilities play an important role in the daily functioning of people in general. However, during the process of aging, there is a decrease in some of these cognitive abilities. Although the cognitive loss associated with aging is a human experience, which differs in extent between individuals, there are similar characteristics in many cases (Wisdom et al., 2012). Cognitive loss can be highly pronounced in skills that require greater levels of mental processing and high levels of cognitive resources (Brailean et al., 2015). Cognitive abilities can be divided into several domains which cover attention, memory, language, praxis and visuoconstructive skills and executive functions (Fuentes et al., 2014).

In aging, the changes seen in attention appear to be of two types, that is, divided and selective attention. The first affects the ability of the individual to focus on two stimuli at the same time, and the second refers to the selection of a stimulus for processing, while the other stimuli are "suspended" (Coutinho, Mattos, & Abreu, 2010; Lent, 2010). The performance of these two activities decreases progressively with age. However, simple attention tasks such as digit extension are maintained in normal individuals up to the age of 80 years (Lezak et al., 2012).

The decline seen in memory function during the process of the aging is the most easily observable, and complaints related to these memory issues may be an important risk factor for mild cognitive impairment (MCI), often followed by dementia in the later years (Jonker et al., 2000; Reid & MacLulich, 2006; Miyagawa & Iwata, 2016). In the study by Jacinto et al. (2008) it was observed that there was a greater proportion

of individuals with subjective complaints relating to their memory, who had mild cognitive decline and dementia, when compared to elderly subjects without any memory issues. The changes caused by aging affect memory skills, producing a consistent decline related to new learning capabilities, i.e. there is a decrease in normal primary storage capacity in the elderly (Murmam, 2015). Historical memories for public events and autobiographical memories (episodic memory) are relatively stable with old age, but the accuracy of source memory tends to decrease (Murmam, 2015).

Language is defined from a person's biological and social background, and in the context of evaluating this cognitive ability, there is no way to dissociate these aspects (Mansur, 2010). Language began to be studied during the research of Pierre Paul Broca, who associated a specific region in the frontal lobe of the left cerebral hemisphere with this function, the research being undertaken by observing patients who all had the same symptoms of aphasia and lesions within the same regions of the brain (Salles & Rodrigues, 2014). However, we do not currently seek to identify a specific region for changes in spoken language (aphasia), but rather look for interrelated neural networks (Vigneau et al., 2006). Aphasias are the most studied language changes. They are not related to the process of language itself, but to connections established with other cognitive abilities, such as memory, attention, and executive functions. Impairments in these abilities interfere directly in the speech production process (Hillis, 2007). In a longitudinal study, it was observed that during the aging process, the cognitive ability that appears most resistant to change is that of language, thus changes in this ability during evaluation can be used as a marker of dementia (Argimon & Stein, 2005). One study found that the changes related to language seen in patients with dementia initiated some twelve years prior to the manifestation of characteristic symptoms, this change being assessed via verbal fluency tests (Amieva et al., 2008).

Praxis and visuconstruction are considered related cognitive functions, because their characteristics involve the accomplishment of voluntary acts at the practical level; from the behavior of dressing and brushing one's teeth, to more complex tasks like three-dimensional drawing (Zuccolo, Rzezak, & Góis, 2010). Apraxia is a term that refers to changes within the brain that are related to the areas responsible for planning and sequencing of a motor function (Sanvito, 2010). In Alzheimer's disease (AD), the changes to executive functions can be observed gradually, and in the initial stages, the most commonly seen involve the ideomotor, which is responsible for the reproduction of simple gestures, such as "good-bye" (Sanvito, 2010; Lima, Servelhere, & Matos, 2012) and the conceptual

inability to relate objects to their functions (Wheaton & Hallett, 2007; Lima, Servelhere, & Matos, 2012).

Changes in visual construction are related to visual capabilities, perception, face recognition, depth, distance and color associations, and these functions are usually evaluated by asking the patient to produce a copy of a drawing or by spontaneous activities like drawing a clock (Dani, 2012). The evaluation of visuoconstructive abilities in the elderly may be associated with the differences seen between types of dementia; for example, the study by Cagnin et al. (2015) found that poor performance in the pentagon design subtest of the Mini Mental State Examination (MMSE) may be related to Lewy Body dementia, whereas the poor memory performance is more likely related to AD.

Executive functions (EF), which play an important role in the processing of other cognitive abilities (Royall et al., 2002), consist of a set of cognitive processes that, through integration, allow the individual to direct behaviors, plan goals and evaluate the efficiency of behaviors in controlling impulses (Malloy-Diniz et al., 2010). In the elderly, alterations in these functions may be a predictive factor for the progression of AD, and in the case of MCI changes in these functions in association with other cognitive domains show a higher progression rate when compared to individuals with MCI and isolated memory deficits (Ganguli et al., 2011; Clarck et al., 2012). The frontal lobe, particularly the prefrontal region, has been related with EF (Kristensen, 2006; Stuss, 2011). In normal aging, the loss of these functions occurs due to chemical and structural changes within the frontal region. However, this loss is slow and gradual, and increases after the age of 70. In people who already suffer with a MCI or dementia process, this loss is seen to be a little faster and more intense (Woodruff-Pak, 1997; Banhato & Nascimento, 2007). A study evaluating the executive function of an elderly population with a mean age of 75 years and a diagnosis of AD revealed that there was a significant relationship between executive dysfunction and functional capacity (Gad, 2011). Findings from this same study pointed out that individuals over 75 years of age show changes in executive functions earlier than usually reported (Gad, 2011). A study by Banhato e Nascimento (2007) showed that age was a significant factor when related to executive performance in the elderly.

In Finland, damage caused by changes in cognitive functions are the main reasons for hospitalization in long-stay institutions for elderly people, with cognitive decline being around 70% for women and 55% for men (Nihtilä et al., 2007), while in Brazil, a study conducted in a long-term institution found that 58.7% of the elderly interviewed had some form of cognitive decline (Oliveira & Tavares, 2014).

There are several factors that may be associated with the progressive loss of cognitive functions in the elderly, and among them is schooling. A study by Mejia-Arango e Gutierrez (2011) found that when assessing 357 cases of dementia and 1,719 cases of MCI, the prevalence of dementia was 5.2%, and the group with the highest level of education had the highest prevalence of dementia. The same study also suggested that there is an increase in the prevalence of dementia with age, that is, people over 80 are more likely to develop dementia. Another factor that has been reported in the literature is the area of residence of the elderly, whereby elderly residents in rural areas have a higher prevalence of dementia (6.24%), when compared to those living in urban areas (4.38%). Other factors include a BMI lower than 18.5 kg / m², problems with sleep, hypertension, quality of life, subjective health status, income and race (Peltzer & Phaswana-Mafuya, 2012).

Geriatric assessments are used to establish the health status of the elderly (Decoster et al. 2015), including assessments of cognitive functions, but these are usually time-consuming tests, which generate discomfort and fatigue on the part of the elderly (Extermann et al., 2005; Yourman et al., 2012). Therefore, there are brief tests which are used for the purpose of screening the mental, cognitive and physical health of the very elderly (Gorestein; Wang, 2016), and the use of these instruments has grown significantly in the area of health within Brazil (Ramos et al., 2012).

The main objective of measuring cognitive performance in the elderly is to differentiate between harmonious aging and incipient morbid processes, allowing estimation of functional capacity and the planning of therapeutic strategies (Matos & Paixão-Junior, 2010).

Neurotrophic factors

Neurotrophic factors are secreted peptides that act as growth factors in the phenotypic development and maintenance of specific cell populations under development within the adult nervous systems of vertebrates (Siegel & Chauhan, 2000). Neurotrophic factors promote the survival, growth, and differentiation of neurons. In addition, neurons that lack the necessary amount of neurotrophic factors die by apoptosis (Mattson et al., 2002). Neurotrophic factors such as the brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) affect not only on cell survival, but also activities such as learning, memory and behavior (Mattson et al., 2002; Allen et al., 2013; Budni et al., 2015).

BDNF is a neurotrophin that promotes synaptic plasticity through the activation of its TrkB receptor. It is well described in the literature that BDNF plays an important role in the survival, differentiation and growth of central and peripheral neurons during their development and adult life, via the activation of its TrkB receptor and consequent activation of signaling pathways which are dependent on this receptor. It has also been shown to play an important role in synaptic plasticity, especially in the hippocampus and cerebral cortex (Kang & Schuman, 1995; Korte et al., 1995; Mcallister et al., 1999; Sohrabji & Lewis, 2006; Budni et al., 2015). BDNF supports the survival and maintenance of sensory neurons, the retinal ganglion, cholinergic neurons, spinal motor neurons and some dopaminergic neurons. A great number of studies have looked at the function of BDNF within the cortex and hippocampus, as it affects neuronal activity and has a unique role in synaptic plasticity. The use and disuse of signaling pathways results in the strengthening or weakening of connections between neurons, resulting in the increase or decrease of synapse formation in dendritic spines and collateral axons. The major strengthening element of synaptic connections involves long-term potentiation (LTP). This neurotrophin has a central role in LTP, which is responsible for both the synthesis and consolidation of new memories (Allen et al., 2013).

Another important neurotrophin is NGF, which was the first neurotrophic factor to be discovered, and is also one of the most studied. It regulates the survival, development and tropism of specific neuronal populations in the peripheral and central nervous system (Levi-Montalcini & Angeletti, 1968; Cirulli & Alleva, 2009; Budni et al., 2015). NGF is produced in the cortex and hippocampus, which are targets of basal cholinergic projection neurons in the forebrain, and has an important role in memory (Allen et al., 2013).

In aging, there is a marked reduction in neuronal plasticity (Burke & Barnes, 2006). Although small changes in hippocampal morphology occur during aging, LTP injury is also known to occur (Barnes, 1994; Pang & Lu, 2004; Rex et al., 2005). In senescence, there is impairment in spatial memory without the evident loss of neurons. These changes are probably associated with a reduction in the levels of BDNF (Gooney et al., 2004; Tapia-Arancibia et al., 2008). Aging may be related to a reduction in the transport of NGF by cholinergic neurons, which contributes to the dysfunction, atrophy and neuronal vulnerability often seen in the process (Niewiadomska et al., 2011).

In 1981, Stanley Appel presented a hypothesis that suggested the involvement of neurotrophic factors in the triggering of neurodegenerative diseases. This hypothesis was titled "A unifying hypothesis for the cause

of amyotrophic lateral sclerosis, parkinsonism and AD.” This hypothesis suggested that each of these disorders could be caused by a lack of a “hormone” or a growth factor, which would normally be secreted by the target tissue of the affected neurons, and transported retrograde after being captured by the presynaptic terminal. In AD, these factors could be impaired in the cortical and hippocampal regions (Appel, 1981).

NGF and BDNF are also important for cholinergic neurons, and in addition, BDNF is equally important for the survival and function of hippocampal and cortical serotonergic neurons. Therefore, deficiencies in these neurotrophic factors may not be the initial trigger of the disease process, but may instead induce an increase in cellular death, resulting in the appearance of the symptoms of the disease, as in AD (Hock et al. 2000; Holsinger et al., 2000; Allen, 2013; Budni et al., 2015).

Conclusion

The result of this review points out that the world population is aging in an accelerated way and during this process of aging there are several changes in the organism of the elderly, among which stand out the cognitive and biochemical, one being directly related to the other. In this case, there is a relation of the neurotrophic factors, which may be responsible for the changes in cognitive functions, specifically spatial memory alterations. In addition, in the alterations of the cognitive functions it is possible to observe damage not only of the memory, but of several abilities that can lead to a greater level of dependence of the elderly.

It is necessary that more studies be carried out with this population, which may trace the elderly with cognitive impairment that may be suggestive or conclusive of a neurodegenerative disease. In addition, biochemical data may contribute to the search for new therapeutic models or early identification for AD or other associated dementias.

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