ISSN: 2469-5858

Correia et al. J Geriatr Med Gerontol 2018, 4:048
DOI: 10.23937/2469-5858/1510048
Volume 4 | Issue 2
Open Access

Journal of
Geriatric Medicine and Gerontology

REVIEW ARTICLE

Age-Related Cognitive Changes: The Importance of Modulating Factors

Rut Correia*[1,2*], Jose Barroso*[2] ***and Antonieta Nieto*[2]

[1]*Facultad de Educación, Universidad Diego Portales, Santiago, Chile*

[2]*Facultad de Psicología, Universidad de La Laguna, Tenerife, Spain*

***Corresponding author:** *Rut Correia, Facultad de Educación, Universidad Diego Portales, 8370076, Santiago, Chile, Tel: +56-2-26765843, E-mail: rut.correia@mail.udp.cl*

Abstract

The study of age-related cognitive changes over the last years reveals a considerable variability in available results. The methodological heterogeneity observed in the aging field can significantly contribute to this observed variability, which creates a confusing scenario for beginners in this topic. The main aim of the present article is to extract a clear depiction of the current state of knowledge about age-related cognitive changes regardless of the methodological approach followed by researchers. In this sense, a specific and differential pattern of impairment seems to be present in most cognitive domains, which highlights the existence of a great intra-domain variability in terms of impairment. We conclude it seems to be enough evidence about the influence of certain modulating factors such as benefit from schooling and gender on cognitive aging, and not taking these factors into account when studying age-related cognitive changes contributes to the scarce agreement found in available results.

Keywords

Aging, Cognition, Neuropsychology, Education, Gender

Introduction

People experience both physical and cognitive changes as their age advances. Regarding the study of age-related cognitive changes a lot of effort has been dedicated to the study of age-related cognitive changes over the last century, and this has resulted in an enormous amount of published material. At first glance this literature could be coarsely classified on the basis of the methodological design used in the studies. In this sense, the study of cognitive aging can be addressed by a longitudinal or a cross-sectional approach. Each of these approaches has different advantages and disadvantages. Cross-sectional studies, which are the most common, have to deal with cohort effects [1] while longitudinal research involves elevated costs, learning effects, etc. [2]. The conclusions drawn from cross-sectional and longitudinal studies are often divergent as the former tend to show greater effects of aging on cognition [3].

On a second level, a deeper review of the cross-sectional literature reveals that those works with a psychological background could be also subdivided into two main groups. On the one hand, there are some studies that seem to follow more experimental paradigms, usually with greater interest in the dissection and detailed analysis of different levels of processing of a particular cognitive function (e.g. working memory) and its interaction with another broader cognitive function (e.g. attention, processing speed, etc.). These works are usually framed in some of the existing cognitive theories about normal aging such as the *Processing Speed Theory* [4], *models of Limited Resources* [5] or the *Effort Hypothesis* [6,7], and their aim often focuses on refuting any of these theories as a suitable explanation for the cognitive changes that take place in the aging process.

On the other hand, there are other studies that seem to come from a clinical neuropsychology perspective. These works usually involve the assessment of several cognitive functions using neuropsychological tests or tasks and batteries, i.e., tests extensively linked to particular neural system functioning. Partial data reports based on cohort comparison from ongoing longitudinal projects are frequently found in these works. This is the

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Citation: Correia R, Barroso J, Nieto A (2018) Age-Related Cognitive Changes: The Importance of Modulating Factors. J Geriatr Med Gerontol 4:048. doi.org/10.23937/2469-5858/1510048

Accepted: June 14, 2018: **Published:** June 16, 2018

case of Van Hooren, et al. [8], who explored how sex and educational level influence the cognitive performance of elderly individuals from the MAAS longitudinal project. Other studies focus on the analysis of differential patterns of impairment throughout modalities within cognitive functions like verbal vs. non-verbal learning, short term vs. long term memory, etc. (e.g. Haaland, Price and Larue, [9]).

The methodological heterogeneity described so far and the significant variability in available results in the study of cognitive aging creates a confusing scenario for beginners in the aging field. Given this situation, we think that it is necessary to extract clear concepts from the current state of knowledge about age-related cognitive changes, regardless of the methodological approach followed by different researchers. With the present work we aim to highlight the role some factors such as education and gender may play in helping to explain the variability found in normal aging cognition.

Cognition and Aging

Processing speed

A decreased cognitive processing speed in old age is currently a widely accepted finding usually related to the changes in the brain white matter that take place in the aging process [10,11]. However, it still remains unclear to what extent this slower processing speed accounts for the impairment of other cognitive functions in aging [12,13]. Authors such as Salthouse [4] argue that the slowing found in normal aging produces a global effect on cognition, so that the impairment captured when performing tasks related to other cognitive domains is better explained by this slowness rather than by a real malfunction in these other domains. As Salthouse suggests, slowness has such an effect because many tasks assessing cognitive domains other than processing speed are time-dependent or require the simultaneity of different cognitive processes. Finkel & Pedersen [14] partially support this hypothesis showing that age-related changes in cognitive domains such as memory, crystallized abilities and fluid abilities are mitigated after statistically controlling for the effects of processing speed. On the other hand, Keys & White [15] also recognize the important role of the speed component but warn that their findings show that processing speed on its own cannot account for all the variance in executive performance seen in normal aging. In this sense, as Wilson, Bienias, Evans & Bennett, [16] claim it seems that slowing in aging is not only person-specific but also domain specific, which means that the percentage of variance explained by processing speed changes in normal cognitive aging may vary, not only among individuals, but also among different cognitive domains in the same subject.

In the light of these results, the current and future challenges regarding processing speed in normal aging should be about clarifying the specific contribution of slowing to the alleged *age-related* changes in the various cognitive processes.

Memory

Many resources have been directed at studying the relationship between aging and memory in the last fifty years. The term *Forgetfulness Benign Senescent* was proposed by Kral [17] to describe those memory complaints involving a transient difficulty to recover any non relevant information for the current context that neurologically intact elders usually experience. The term *Age Associated Memory Impairment*-AAMI [18,19], also emerged in the following years and being widely accepted by aging researchers generated a large number of studies. Even though issues such as the AAMI prevalence and outcome are still inconclusive [20], their proponents defended AAMI as a memory impairment associated to the normal physiological aging process and not related to an age-related disease [21]. These first attempts at describing age-related memory changes were not very accurate in terms of depicting the memory systems and components involved, which might be associated to a shared belief about most of these memory components being somehow affected by age [22]. Nonetheless, current reviews indicate that the memory impairment in normal aging is not widespread, but it is specific to certain sub-systems or components [23,24]. Thus, it appears that older adults show difficulties when carrying out certain tasks of memory and learning, while their performance in other tasks is comparable to that of young individuals.

Several works find a negative age influence on the Hanoi Tower [25-28], suggesting impairment of procedural learning (the ability to acquire new habits and skills through practice) in aging. Nonetheless, some authors warn about the great demands in terms of executive functions, processing speed and visuospatial skills that tasks like the Hanoi Tower have [24,25]. Thus, the relationship between aging and procedural learning has not been fully understood yet and further studies are needed to clarify its nature [24,29].

Focusing on declarative memory in normal aging, studies report greater episodic than semantic memory impairment [24,30], suggesting that a semantic memory impairment might be more related to pathological age-changes [23,31]. Therefore, it seems that when the literature refers to normal aging memory impairment it frequently means normal aging episodic memory impairment. In this regard while some studies have reported an age-related decline on memory recall, both immediate and delayed [24,32], others argue that poor delayed recall is largely explained by a previous low immediate memory performance [9]. This kind of controversy has led the discussion to focus on the differential involvement of memory processes such as encoding, storage and retrieval. So far, most authors agree about the greater impairment of encoding and retrieval compared to the information storage in normal aging [28,33,34]. Supporting this view, some recent studies have shown that providing older adults specific encoding strategies such as visual representations or semantic associations improves their memory performance to the young adults' level [35,36]. Thus, these memory difficulties described in normal aging seem to be more associated with executive impairment than with hippocampal involvement [37-39].

Visuoperceptive, visuospatial and visuoconstructive skills

Age-related changes in visuoperceptive, visuospatial and visuoconstructive skills are not widespread but, once again, show a selective and specific pattern [40]. Simpler and more passive visuoperceptive skills based on the discrimination of specific visual features such as shape, color, brightness, etc., do not appear to be significantly affected by age [41]. Works like Viggiano, Righi & Galli [42] suggest that even when older people show a poor performance in visuoperceptive tasks, variables other than those related with visual processing such as the semantic category of the stimuli and the familiarity of the represented concepts may explain their execution.

Visuospatial functions are understood here as the ability to establish relationships or judgments about elements based on spatial features such as their position, orientation, movement, etc., are impaired in normal aging [40]. Age effects on visuospatial tasks have been found not only in experimental settings or psychometric assessments but also in more ecological settings where patients are asked to self-orientate and navigate in a three-dimensional space [43].

Performance in visuoconstructive tasks, which requires a proper coordination and integration of visuoperceptive and visuospatial abilities with motor and manipulative skills, such as copying drawings, building block designs, etc., is also poorer in elders [44,45]. Nevertheless, performance in visuoconstructive tasks is also dependent on other variables such as speed of processing, sensory deficits, familiarity, etc. Therefore, several authors highlight the importance these confounding factors have when assessing older adults' performance in visuoconstructive tasks [9,22,46]. In this regard, Ogden [47] reports elders' poor performance in these tasks might reveal executive but not visuospatial and visuoconstructive difficulties, since their performance improves when they receive external guidance to structure the task. Results obtained by Jefferson, et al., [48] support this argument. These authors assess visuospatial functioning with the Hooper Visual Organization Test [49] in 222 healthy older individuals and found that 12% of the accounted variance is explained by the participant's performance in COWAT without any significant contribution of the semantic fluency task. Thus, they conclude that in normal aging, measures of executive functioning are the best predictors for visuospatial performance.

It seems to be generally considered that there is a greater impairment of visuoperceptive and visuospatial skills versus other cognitive domains such as language in normal aging [50]. However, before perpetuating this statement it should be noted that many results supporting this come from studies addressing this issue by comparing elders' performance in verbal memory tasks with their performance in visual memory tasks [51-54] and few compare tasks without memory load. In addition, tests traditionally used to measure language skills match those designed to assess crystallized intelligence, while those assessing visual skills represent measures of fluid intelligence. In this case, the results would only be pointing out that there seems to be a greater deterioration in fluid than in crystallized intelligence in normal aging [55]. Finally, age-related sensory deficits and their influence on cognitive performance should also be considered before drawing conclusions about visuoperceptive and visuospatial abilities in normal aging [56-59].

Language

Best preserved functions in aging appear to be linguistic ones [60]. Some authors even suggest that certain semantic and vocabulary skills can potentially increase with age [61,62]. However, when compared to their younger counterparts, those language skills requiring preserved lexical access and retrieval seem to be more affected in older individuals. Although these processes can be examined in spontaneous speech [63,64] most results come from word generation paradigms such as confrontational naming of pictorial stimuli and cued verbal fluency. As regards confrontational naming, most studies support age-related changes [65-68]. It has also been frequently reported that elders' performance in this task significantly improves when phonetic cues are given [65,69,70]. Thus, it seems that healthy elders' deficits in confrontational naming are related to impairment in the accessibility of the words' phonological form (lexical access) rather than to a loss of the words' meaning. Impairment of semantic knowledge has been more closely associated to some pathological manifestations of aging [31,71,72]. It has also been proposed that the grammatical nature of the naming task stimuli plays a relevant role in the elders' performance. Although some authors have reported a greater impairment of naming nouns compared to verbs in normal aging [65,70] the inequality of the materials employed in these studies does not allow one to come to such a conclusion. Indeed, when these methodological limitations are overcome, confrontational naming skills in normal aging are not differentially affected by the grammatical nature of the stimuli [69].

Cued verbal fluency has also been widely studied in normal aging. Cued verbal fluency is a language production task requiring preserved lexical access for it to be successfully performed. However, as this demands an active search of information following a particular cue, this task also recruits other cognitive domains such as focalized and sustained attention, processing speed, strategies generation, response inhibition, working memory, etc. In this sense, cued verbal fluency is mainly considered to be a valuable task for the assessment of executive/frontal function [50]. Age-related changes in cued verbal fluency is a well-documented effect [73-79]. Although further efforts are needed to clearly demonstrate and comprehend it, some authors have reported a differential involvement depending on the cue type. It seems that older adults exhibit a poorer performance in semantic fluency but are as good as their younger counterparts in phonetic fluency [61,80-82]. Nonetheless, other works fail to find this differential impairment [83]. More qualitative approaches such as those proposed by Troyer, et al. [82], where performance strategies in verbal fluency tasks are examined, may shed some light on this controversy.

Although still largely unexplored, language comprehension in normal aging has been gaining more attention recently. A special focus has been placed on the effects of the aforementioned age-related sensory deficits. In this regard, Burke & Shafto [84] conclude that there is strong evidence supporting the notion that the decline in visual acuity affects the linguistic performance of older adults. They also indicate that when stimuli intelligibility is assured for every age group, most differences between their performances in language comprehension disappear.

Attention and executive functions

Far from being a unitary function, attention is comprised of different types of processes and systems. At least three kinds of processes can be distinguished: those that establish and sustain a vigilant or alert state, those that orientate towards the selection of relevant information from sensory input and thirdly, those more related to attentional control, monitoring attentional resources and solving conflict among responses [85-87].

Basic attentional functions related to the alerting and orienting systems show a relative preservation in normal aging when compared to the age-related deficits found in those more associated to the executive components of attention [88-90]. However, results regarding tasks involving conflict, such as selective attention tasks, are not convergent [90-92]. Authors such as Kramer & Madden [93] conclude that while selective attention deficits in normal aging exist, they do not follow a unique pattern of involvement. In this sense, authors distinguish between first, the ability to highlight a stimulus or relevant information from environment distractors and second, the ability to inhibit this other non-relevant information, such as the main components of selective attention tasks. The attentional impairment associated with normal aging seems to be more related to the component of inhibition than the distinction of the relevant stimuli [88,94-96]. The higher attentional cost this kind of task has for older adults is linked to the age-related changes in the frontal lobes and executive functions [93,97]. The term *executive functions* is a construct that includes a wide range of specific cognitive processes such as complex attentional processes and inhibitory control, working memory and prospective memory, concept formation, abstract reasoning, cognitive flexibility, decision making and problem solving, etc [50]. This construct is broadly used as a synonym for the term prefrontal or frontal functions, but this assumption is still controversial [97,98].

Deficits in inhibitory control affect the elders' performance beyond attentional tasks. For instance, they may also affect working memory and memory recall. In this sense, difficulty in inhibiting irrelevant memories actually interferes with the retrieval of relevant memories [95].

Working memory can be conceptualized as a system to retain and manipulate information temporarily. It is a basic cognitive function recruited by other more complex cognitive processes [99]. This system involves two main components: a) A primary component responsible for simply keeping the information available for a short period of time, and b) A second component of "actual" working memory, which not only keeps but also manipulates that information [23]. There is considerable variability regarding working memory findings in normal aging. Studies with more demanding working memory paradigms report more consistent results [100,101] than those where simpler tasks like verbal or visuospatial span are administered [41,44]. Thus, it seems that while the primary component of working memory is not greatly affected by age, the impairment of the most complex component with a greater executive load is a convergent finding [23,102].

The ability to remember that one has to do an activity at a particular time in the future is known by the name of prospective memory. Prospective memory is contemplated within executive functions due to its high standards in terms of self-regulation skills, time management and control, as well as strategy generation. Prospective memory has recently received much attention given its implications for functional independence in elderly peoples' daily lives. Therefore, there is evidence of its decline [103] but also of its preservation [104]. Nonetheless, a meta-analysis study conducted by Henry, MacLeod, Phillips & Crawford [105] shows that while in most laboratory settings elders show a certain degree of prospective memory impairment, efforts to assess it in more ecological scenarios fail to find any decline. Thus, subtle prospective memory deficits found in experimental situations do not seem to interfere with elderly peoples' everyday lives.

Finally, based on a poor performance in the Test Wisconsin Card Sorting (WCST, [106]) some authors have suggested impairment of concept formation in aging [107]. However, some works argue this poorer performance is more related to the loss of mental flexibility found in aged people [108]. It is precisely this loss of mental flexibility which is also associated with other executive deficits in normal aging such as strategy generation and organization [109].

In summary, despite the diversity of results found in the literature, some findings regarding changes across different cognitive domains in normal aging seem to converge to a pattern of impairment characterized by a slowing in processing speed, memory deficits related to difficulties in generating strategies to achieve an adequate encoding and/or spontaneous recall, controversial results regarding visuospatial and visuoconstructive deficit confounded by important executive, speed and sensory requirements of the assessment tasks, an overall linguistic preservation with specific impairment of those more self-driven production components, and various difficulties in the spectrum of the so-called executive functions. Thus, these deficits seem to be especially related to processes such as cognitive control, regulation and planning within each cognitive function. Therefore, this pattern of impairment suggests a special engagement of functions closely related to frontal lobe function with both cortical and subcortical involvement [110-112].

Modulating Factors in Normal Cognitive Aging

As mentioned above, there is a set of variables that might be contributing to the aforementioned heterogeneity between results regarding cognitive aging. These variables seem to be factors that modulate the probability of occurrence of age-related cognitive decline. Thus, they may play a protective or facilitator role in terms of damage risk [41,113,114]. Factors that have received most attention are overall health status (e.g. cardiovascular risk, diabetes, etc), genetic factors (APOE e4), physical activity, and psychosocial and demographic factors (e.g. education, gender). The great impact of health and genetic factors on cognitive aging has been widely acknowledge [30,115-118], thus our aim here is to focus on psychological and demographic factors.

The role of schooling as a protective factor against the development of neurodegenerative diseases associated with aging, especially Alzheimer's disease, has been widely described [119-123]. Moreover, Ardila & Roselli [44] even reported that during normal aging the education is more influential on neuropsychological performance than the age itself. Nonetheless, the particular effects that schooling has on different cognitive functions have not been extensively studied. Although many studies have collected information regarding educational attainment as a demographic variable not many of them assess how this variable may affect cognition in normal aging [115]. Once again it seems that schooling does not have a generalized effect on cognitive aging, but it is very dependent on the cognitive domain assessed. In this sense, the study presented by Ardila, et al. [45], following the research line initiated by Capitani, Barbarotto & Laiacona [124], shows different patterns of relationship between age and education in normal aging depending on the cognitive function analyzed. So, this relationship could be one of *parallelism,* where age changes are of similar magnitude in high and low education participants, of *protection* where the magnitude of the age-related changes are significantly lower in the higher education group, of *confluence upwards* where scores from both educational groups tend to converge with advancing age because the low education group scores largely increase and *confluence downwards* where the convergence is due to an age-related decrease in the high education group performance. Although the last two patterns could seem counterintuitive, they should be interpreted in a framework where not only cognitive decline, but also cognitive development is associated with education. Therefore, the *confluence upwards* pattern reflects those skills that can be compensated with later experience in the absence of an effective early education. On the other hand, *confluence downwards* is related to those functions where low educated individuals' performances exhibit a floor effect that cannot be compensated by later life experience. Ardila, et al. [45] also warn that many of the cognitive measurements assessed could not be identified with any of the patterns described above, pointing out a complex relationship between cognition, age and education. This complexity probably contributes to the lack of agreement about the influence of education on cognition in normal aging. Thus, while several results defend a significant influence [125-128] others fail to find it [129].

This variability described above has also led some authors to suggest other measurements that might better represent the achievement and benefit from schooling than educational attainment or years of schooling *per se*. Some literacy measurements have been proposed in recent works [130,131]. This kind of measurement takes into account that not all individuals who have met a certain grade level have achieved the same amount of learning, and that not the whole educational experience comes from years of formal schooling [132]. Therefore, literacy tests can be used to control variables such as the quality of the learning experience.

Very recent works support this lack of validity of formal education measurements particularly in older populations [133,134]. Although there are still not many studies administering culture-based tests to assess the effect of education on cognitive function in normal aging, results so far look promising. Barnes, Tager, Satariano & Yaffe [135], show that scores in a literacy test (NAART, [136]) are better predictors of cognitive functioning than educational attainment in a sample of well-educated adults. Manly, et al. [131] have found that, compared to years of schooling, reading skills (WRAT-3, [137]) significantly better explain differences in cognitive performance between Afro-American and white elders. Reading skills also significantly better predict the rate of memory decline in a 5-year follow-up [132]. In addition to literacy tests, the WAIS-III Information subtest has been recently proposed as a useful tool to assess educational achievement in other populations, especially when it is intended to study subjects coming from different educational systems and qualities, in languages where literacy tests are not that reliable [138]. These authors found that Information subtest score is more strongly associated with neuropsychological functioning than education in older Spanish adults.

Gender difference is gaining more attention as a modulating factor in cognitive aging, which is probably influenced by the common assumption that women are less vulnerable to age-related brain changes than men [139]. Some studies do not agree with this idea finding no significant differences in rates of cognitive decline between men and women [140-142], others report that men exhibit higher rates of decline than women in certain cognitive domains [143-145] and some even present results in the opposite direction [146]. On the other hand, when analyzing gender differences on cognitive performance of healthy elder's significant differences usually appear. So, while men mainly outperform women in visual tasks [140,142,146], women perform verbal memory tasks [8,140-142,147,149], verbal fluency [76,140,143,146,148,150] and some cognitive speed measures significantly better, even when they have fewer years of formal education than men [149]. In fact, some works report that when accounting for educational level and health measurements, far from disappearing gender differences are maximized in favor of women [141,149]. Thus, it seems that gender is an important factor to account for when studying cognitive aging, however very few is know about the interaction of gender and other measurements that better apprehend the educational experience yet.

Conclusions

In summary, the literature reports a considerable variability regarding the relationship between aging and cognitive functioning to the extent that some findings even seem contradictory. In this sense, we believe that conceptualizing cognitive functions such as uniform domains, supported by a unique system, might help to nourish this variability. Taking memory as an example, it would be a mistake to come to conclusions about the overall memory functioning in normal aging from partial results regarding specific memory measurements (working memory, immediate memory, delayed, verbal vs. non-verbal, etc.). As the higher cognitive functions have been conceptualized as complex processes or systems that bring together different components [50,87,151], authors have realized results about age-related changes in cognition have represented a differential involvement of the components and processes recruited by these functions. Thus, this specific and differential pattern of impairment seems to be present in most cognitive domains (processing speed, memory, visuoperceptive, visuoconstructive and visuospatial capabilities, language, attentional and executive functions). Intra-domain variability is such that even in a domain such as language some aspects decline (e.g. fluency) whereas other may improve (e.g. vocabulary) in normal aging. Nonetheless, many findings seem to agree with the notion that frontal lobe components are the functions most affected by the age-related changes across different cognitive domains. In addition, although a considerable heterogeneity in the results has been associated with the cognitive variability inherent to the study sample, another significant amount of variability seems to be explained by methodological differences among studies. In this regard, there are certain factors such as literacy and gender that have proved capable of explaining the significant variance of elders' cognitive performance but that unfortunately are frequently omitted in cognitive aging studies. Nowadays, there is already enough evidence to think that not taking these factors into account can lead to misleading conclusions about age-related changes in cognition. Thus, in order to improve our understanding of how age affects cognitive function, worldwide future research in the cognitive aging field should consider the differential and specific effects that age seems to have on cognition, as well as the relevance of education and gender as important modulating factors.

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