

Title: Longitudinal trajectories of cognitive aging

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ABSTRACT

Purpose of review

This review summarizes recent evidence related to the cognitive trajectories of aging, the factors associated with the different trajectories, and the effect of sex on cognitive decline.

Recent findings:

Trajectories of cognitive aging identified in different studies vary in number, in the proportion of individuals falling into each of the classes and in the predictors of class membership. Trajectories observed include types with 'rapid decline', those with 'gradual decline' and those with 'maintenance of high level' of cognitive performance. Predictors of decline and predictors of maintenance of cognitive performance may be different. While factors such as education were in general associated with high performance, and reversely with low performance, other factors, such as depression were predictors only for some groups, particularly the declining ones. Sex differences in cognitive trajectories and the associated predictive factors have also been identified.

Summary

The findings on education may be particularly important in populations with low educational level, especially among women and the findings on depression have special interest in preventing cognitive decline in women. Further work is required to explain intriguing inconsistencies observed in the literature.

Keywords: Cognitive aging, trajectories, sex differences, education, depression

TEXT

Introduction:

In a background of increasing interest in cognitive function, a major determinant of healthy aging [1], this review summarizes evidence related to the careful analysis of cognitive paths (trajectories). We have paid special interest to those studies producing groupings of participants based on the pattern of cognitive change over time. Longitudinal repeated cognitive assessments are better than a cross-sectional measure to capture the natural process of cognitive aging over time and to understand the complex and subtle variations across the lifespan. Furthermore, identifying latent (unknown a priori) classes of cognitive trajectories by classifying and clustering the participants with similar cognitive trajectories provides a more comprehensive knowledge of the natural process of cognitive aging, as takes into account the intra-individual change as well as the inter-individual differences [2]. The review also addresses the factors associated with the cognitive path, and with the different trajectories, particularly the potentially modifiable factors. Moreover, in the background of the urgent need “to bring sex and gender into the mainstream of modern medical research” [p.577] [3], this review also focuses on the effect of sex on cognitive decline, which needs clarification. Furthermore, some health outcomes related to cognitive trajectories are analyzed.

Cognitive aging

~~However,~~ Contrary to traditional knowledge suggesting a decline of cognitive function with age, recent evidence shows between-individual differences in the “age” pattern of deterioration [4]. Some of the most recent studies investigating trajectories, considered as the course of cognitive function over time or age, have used two or more waves of data, and methodologies that take into account the heterogeneity of the populations. These studies show that age-related cognitive changes are relatively slow but start in midlife [5], around the fourth decade of life [6], and that differences in cognitive scores reach significance every two decades throughout

different age groups [5]. Still, some longitudinal studies show an acceleration of cognitive decline in the seventh decade of life [6].

The last reports focused on describing the distinct trajectories in individuals, with heterogeneous classes of longitudinal changes in cognitive performance, have used Mixture Models (Growth Curve Models and Joint Latent Class Model) as statistical methods. These studies based on community-dwelling older adults and using general cognitive tests or composite scores to assess cognition describe two or more possible cognitive trajectories [7–11], consistent with previous data [2].

The trajectories identified include types with maintenance or with different degrees and rates of decline of cognitive performance (Table 1). The proportion of the sample classified into each of these classes also varies, for example, the “declining group” includes a range of 5.3 to 26.9% (Table 1).

The differences between studies are intriguing and may be influenced by the method of cognitive assessment and characteristics of the sample. Walsh et al. defined three cognitive trajectories in a sample whose cognitive status was assessed through a standardized telephone interview over 12 years, with 19.6% of the subjects included in the trajectory with a more precipitous rate of decline [12]. Nevertheless, no trend is observed in the number of trajectories identified based on the sample size, sample characteristics or baseline age.

On the other hand, the optimal number of classes identified by the statistical technique is not determined based on a single objective criterion but derives from a combination of subjective judgment and objective statistical indices, which may contribute partially to the variance observed. Despite this, most studies identified a remarkable proportion of individuals who maintain their cognitive function through aging, which can be considered an important attainment of the methodology used which broadens our knowledge on successful cognitive aging.

Cognitive domains and cognitive aging

Recent studies also confirm that some cognitive functions could lose a significant proportion of their initial ability with aging, but other functions remain relatively preserved. However, mental processes interact between them, and some functions may influence cognitive aging. Some theories suggest a major role in sensory processing, working memory, or executive control ability, which includes the effectiveness of inhibiting irrelevant information [13].

Related to attention, some inconsistencies are observed in the literature. In some reviews, all aspects of attention have been considered to decline with aging, due to age-related frontal lobe degradation. Novotny et al. found that attention scores were quite homogeneous between the oldest groups of their study, suggesting that attention is relatively preserved compared to other cognitive domains [5]. However, Zhao et al. reported that measures depending on executive attention are more significantly affected with age, such as divided attention, especially in complex or dual tasks [14].

Memory has been one of the most studied domains in cognitive aging research. However, memory is not a unitary concept and different areas must be considered. Working memory is affected to a greater extent than short-term memory; and shows the most extensive changes between individuals after the age of 60 years [5]. Declarative memory declines much more than implicit memory [14]. Episodic memory may be significantly impaired as people age [6], in contrast with semantic memory, which may hardly be affected by age-related cognitive decline [14]. Memory decline has been considered to be associated with damage of subcortical white matter, and closely associated with hippocampus atrophy.

The processing efficiency and speed of executive function tend to decrease with age [14] and show great variability among aged people [5]. Atrophy of gray matter in the prefrontal lobe and damaged structural integrity of subcortical white matter are related to a decline in executive function and processing speed [14].

The general linguistic ability remains stable as people age. An exception has been observed with a trend of decline in verbal fluency, which involves also executive functions such as monitoring

previous responses and blocking intrusions from other semantic categories [14]. Atrophy of the bilateral insula is mainly related to deficits in word recall and generation [14]. The physiological changes documented in the brain during normal aging need consideration concerning decline of cognitive function: (a) decrease of volume of grey matter, that occurs linearly across the life-span; (b) changes in the integrity of white matter fibers, which increases before the age of 40 and decreases after 60 years; (c) loss of functional specificity in the brain region during task performance in the elderly (dedifferentiation and reduction of hemispheric asymmetry), due to deficits in the dopamine regulatory system; and (d) disconnection of large-scale brain networks, such as the default mode network and the salience network [14]. However, the brain may respond to these changes by generating “scaffolding” [13] through the recruitment of more neural resources and other brain areas to compensate for lost functions or reorganization of the whole-brain connectivity pattern [14]. Therefore, the behaviors of older adults may be maintained at a similar level than those of younger people due to this homeostatic phenomenon. Unfortunately, the aged brain is less efficient at generating scaffolding, especially under pathological conditions such as Alzheimer’s Disease, and scaffolded networks are only efficient at the easier task levels [13].

Predictors of cognitive aging trajectories

Recent evidence supports the idea that cognitive aging is a dynamic process where aging-related cognitive decline has complex interactions with other biological and psychosocial changes [14]. Therefore, the individuals’ lifelong development and experiences must be considered [13]. Yang et al. have found a more favorable aging-related cognitive change across 20th century birth cohorts (higher average cognitive abilities and slower rates of decline) related to previous generations, which probably reflects socio-cultural influences due to advances in educational attainment and associated protective factors[6].

Among the factors predicting cognitive aging, education and cognitive reserve have been consistently associated with better functioning and maintenance [15][10][16][17]. CR is

considered to be the ability to maintain cognitive performance despite brain pathology. CR is built through life-course experiences (including education) and is a key construct in promoting healthy aging [18]. While there is limited evidence on the association of CR and specific cognitive trajectories, one recent study shows that even in the presence of brain pathologies, a high CR indicator was associated with preserved global cognitive function, and also with specific functions such as episodic memory, and working memory [19].

Recent studies also support the notion that predictors of class membership are different for each pattern of cognitive aging. This is evident when there are at least three trajectories identified and there is a statistically significant comparison for each category with the others. Although inconsistencies have been observed in the literature, in general, some factors, particularly a higher level of education, predicted being in the trajectory groups who maintain their cognitive performance and a lower level of education predicted belonging to the class with clear cognitive decline [10,11]. However, a different pattern has been observed for other factors. Specifically, depression, diabetes, dependence on iAVDs, alcohol consumption, smoking or obesity were predictors only for some groups [11]. For example, in the study of Wu et al. [10], when comparing average performers, living alone and dyslipidemia each only predicted an increased risk of low cognitive performance but were not associated with less likelihood of being a high performer, while diabetes and depression, and in particular hypertension and obesity, predicted a decreased likelihood of being a high performer, but were not associated with low cognitive performance. Similar observations have been reported before, and this might have important implications, since looking for mechanisms of cognitive maintenance and resilience might not simply be to look for the opposite of those identified as risk factors for deterioration [10].

Among other factors associated with preserved cognitive function, there is evidence about enriching activities and physical activities across the lifespan, which might be beneficial for preserving cognitive functions [20,21]. On the contrary, a recent study has shown that

multimorbidity accelerates cognitive decline in older adults and specific disease combinations have a different impact on cognitive trajectories [22]. In this study, the neuropsychiatric, sensory impairment/cancer, and cardiovascular patterns showed the worst prognosis.

While these are important findings, Zheng et al suggest that future research is needed to discover the main determinants of the slope of cognitive decline as they showed that factors such as education, socioeconomic level, race, depression, ADLs, and others explained only 5.6% of the variation in the slope [17]. The addition of biomarkers may certainly improve the prediction ability to predict cognitive decline [9][23], and introduces interesting, potential lines of research.

Sex differences in cognitive aging trajectories

In a background of increasing medical interest in sex differences related to various conditions, the available information directly related to sex differences in cognitive trajectories in healthy aging has been considered limited and still controversial. Nevertheless, recent studies tend to confirm small but significant differences in cognitive aging between sexes. Women may have more cognitive reserve but faster declines than men [24][25][26][27] and men a better preserved cognitive function at old age [21].

In the last two years, there are studies analyzing independently the results in men and women that support relevant differences in cognition, such as the rate of decline [16,21,25–28], the cognitive domains affected [25,27,28]; the number of trajectories [16], the proportion of individuals with significant decline [16] or the predictive factors associated with the different trajectories identified [16]. We have shown that cognitive decline might not be so common as supposed. This was more evident for men, whose proportion of maintainers were approximately 80%, compared to women (50%) [16].

Several studies show that at middle age women have better cognitive function than men [24,27,28] while others explain that the verbal advantage of women could lead to a delayed

diagnosis of impairment [29]. However, the rate of decline through aging was higher and steeper in women, in several studies [16,21,25–28].

Those studies analyzing specific cognitive domains have shown in women a faster loss in information processing speed [27], verbal fluency and fine motor skills [25,28,30]; and consistently a more rapid decline in memory [25,27,28]. Only two recent studies have analyzed separately the intra-sex variability in the grouping of trajectories of cognitive aging. Suo et al. observed 3 classes in both men and women [21], but in the study of Lobo et al, men showed more heterogeneity as they grouped in 4 classes while women grouped in only 3 classes [16].

Finally, sex differences in predictive factors of cognitive aging have also been documented. It has been suggested that a better socioeconomic status and education level can benefit more to women [16,26]. Related to cardiovascular risk factors of cognitive decline, diabetes has been negatively associated only for men in Bonberg et al study [28], while only for women in Lobo et al [16]. On the contrary, obesity was found as a predictor of decline only for women and treated hypertension was positively associated for men but negatively for women [28]. And the negative impact of depression in cognitive trajectories has been observed in women but not in men [16].

Assuming that the sources of the sex and gender differences in cognitive aging are not fully understood, the latest attempts have provided some hypotheses. Females show verbal advantage that could lead to a delayed detection of decline compared to males, and subsequently to a more rapid rate of deterioration and diagnosis of dementia for them [29]. This would be compatible with the fact that sex moderates the association between imaging measures and function, because women are more resilient to brain pathology [29]. Sex differences in cognition might be partially explained by biological factors in addition to hormonal factors, such as differences in connectivity: females show greater efficiency in frontal executive networks, whereas males show greater efficiency in the posterior default mode network [29].

Cognitive trajectories, dementia, and health outcomes

Cognitive trajectories in older individuals have likewise been studied recently concerning clinically relevant health outcomes. A rapidly decreasing cognition may be related to an increased risk of incident dementia [12,31,32], but also to an increased risk of frailty and balance impairment, disability in activities of daily living (ADL), and the Motor Cognitive Risk Syndrome [7]. In contrast, those who remained largely stable with little decline over time, “optimal cognitive aging” had almost no cases of dementia and the lowest rate of death in a 12-year follow-up [12].

The trajectories of individual cognitive functions have also received attention in the literature. The risk of mortality was increased for subjects with the worst episodic memory trajectory[31], and dementia was predicted by trajectories of all cognitive tests, but the worst performers of episodic memory and psychomotor speed had respectively a 37-fold and 33-fold increased risk of dementia compared to those who maintained high cognitive performance [31]. Consistently, Payton et al. observed that declining fast in three or more cognitive functions had a 4- times higher risk of dementia [32].

Conclusion

Distinct cognitive trajectories have been identified in different studies, varying in number and the proportion of individuals falling into each class. Potentially modifiable predictors of class membership have also been identified, but predictors of decline and maintenance of cognitive performance may be different and not just simply opposites. Between-cognitive domain differences in degree of decline have been documented. Furthermore, sex differences in cognitive trajectories and the associated predictive factors have been identified, the deleterious effect of both low education and depression being more apparent in women. A rapidly decreasing cognition has been found to be associated with an increased risk of dementia and similarly with other negative health outcomes. New studies should try to explain inconsistencies observed in the literature, and those focused on individuals with good and stable cognitive performance are promising.

Key points:

- Distinct trajectories of cognitive aging have been identified in different studies, varying in the number and proportion of individuals falling into each class.
- Education was generally associated with high performance and reversely with low performance.
- Factors such as depression were predictors only for some groups, particularly the decliners.
- Predictors of cognitive decline and of maintenance of cognitive performance may be different.
- Sex differences in cognitive trajectories and the associated predictive factors have been identified.

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