Age-related episodic memory decline and the role of amyloid-β: a systematic review

Jandirly Julianna Souto1,2, Gabriella Medeiros Silva1,2, Natalia Leandro Almeida1,2, Irina Ivanovna Shoshina3, Natanael Antonio Santos1,2, Thiago Paiva Fernandes1,2

ABSTRACT. Aging has been associated with the functional decline of episodic memory (EM). Unanswered questions are whether the decline of EM occurs even during healthy aging and whether this decline is related to amyloid-β (Aβ) deposition in the hippocampus. Objective: The main purpose of this study was to investigate data on the relationship between the age-related EM decline and Aβ deposition. Methods: We searched the Cochrane, MEDLINE, Scopus, and Web of Science databases and reference lists of retrieved articles that were published in the past 10 years. The initial literature search identified 517 studies. After screening the title, abstract, key words, and reference lists, 56 studies met the inclusion criteria. Results: The overall results revealed that increases in Aβ are related to lower hippocampal volume and worse performance on EM tests. The results of this systematic review revealed that high levels of Aβ may be related to EM deficits and the progression to Alzheimer’s disease. Conclusions: We discussed the strengths and pitfalls of various tests and techniques used for investigating EM and Aβ deposition, methodological issues, and potential directions for future research.

Keywords: memory, memory, episodic, aging, healthy aging, beta amyloid, systematic review.

INTRODUCTION

Aging has been associated with a functional decline in episodic memory (EM). An assessment of the memory function in healthy aging can represent a meaningful alternative since Alzheimer’s disease (AD) tends to be diagnosed at more advanced stages, especially when memory impairments appear. Approximately, 30% of elderly individuals with normal aging, above 60 years old, can have high levels of amyloid-β (Aβ) deposition in the hippocampus.1 Hence, they tend to be more likely to develop AD.2

The systematic review was conducted by the Universidade Federal da Paraíba, João Pessoa, PB, Brazil, and Pavlov Institute of Physiology, St. Petersburg, Russia. 1Department of Psychology, Universidade Federal da Paraíba – João Pessoa, PB, Brazil. 2Perception, Neuroscience and Behaviour Laboratory, Universidade Federal da Paraíba – João Pessoa, Brazil. 3Laboratory of Physiology of Vision, Pavlov Institute of Physiology – St. Petersburg, Russia.

Thiago Paiva Fernandes. Cidade Universitária, S/N – Castelo Branco – 58051-900 João Pessoa PB – Brazil. E- E-mail: thiagompfernandes@gmail.com

Disclosure: The authors report no conflicts of interest.

Funding: none.

Received on September 16, 2020. Accepted in final form on February 22, 2021.
Age-related memory decline, especially in those related to EM, is common in aging, and Aβ deposition has been associated with a progressive conversion to AD. EM can be understood as the integration of the “what,” “when,” and “where” (or “which”) components, which is a substantial factor in the social life of an individual. However, it is unclear whether hippocampal volume atrophy and age-related EM decline in healthy aging are entirely related to the deposition of Aβ. One of the reasons is because there are links between the neocortex and the hippocampus. In this way, it is essential to understand the relationship of the hippocampus with Aβ deposition to further unravel the other areas related to EM.

The hypothetical model of biomarkers in AD indicated that the presence of Aβ is related to the functioning of the vascular systems and growth. This model describes the integration of AD biomarkers, which may reflect an underlying pathophysiological sequence of the following events: (1) the presence of amyloid-β42 in the cerebrospinal fluid (CSF) is first detected (the same is true for tau blood biomarkers); (2) levels of tau protein in CSF are significantly increased; (3) hypometabolism of fluorodeoxyglucose occurs; (4) brain atrophy occurs; and (5) cognitive decline is noted.

The model of biomarkers in AD suggests that the relationship between Aβ and cognitive impairment is not immediately successive, and therefore it should be less evident than the relationship between neurodegenerative biomarkers and cognitive impairment. Notwithstanding, the deposition of Aβ before the clinical diagnosis of AD remains a challenge, since less, if any, relationship between a decline in cognition in healthy aging and the deposition of Aβ in the hippocampus can be observed. In this manner, it is comprehensible that cortical thickness exerts a substantial influence on Aβ deposition and the consequent decline in EM.

Age-related dementia typically begins slowly and gradually with brain atrophy before the onset of clinical symptoms. Some authors have suggested that the cognitive decline in aging is related to undetected diseases and, hence, is not a characteristic of normal aging. An important implication of detectable brain atrophy and dementia is that some cases with undetected diseases can help create inferences about normal brain aging. This is of particular concern, since the proportion of elderly people with undetected neurodegenerative disease is expected to increase, potentially leading to baseless conclusions of accelerated age-related decline in the cortical areas vulnerable to disease pathology, especially in the entorhinal cortex and the hippocampus.

Therefore, the contribution of latent pathology to age-related decline in healthy aging remains an open question. However, differences in AD biomarkers, such as brain atrophy and Aβ deposition, may clarify this issue. This review is based on the assumption that the presence of Aβ in people with healthy aging can serve as a prodromal state of AD. Thus, brain atrophy and Aβ deposition are biomarkers of the disorder. Here, our main purpose was to investigate the data on the relationship between EM and Aβ deposition in healthy aging.

**METHODS**

**Search strategy**

The PRISMA guidelines were used. Exhaustive electronic searches were conducted on the studies that were published from 2010 to 2021 in the following databases: COCHRANE, Medline, Scopus, and Web of Science (PROSPERO: CRD42020190981). The following search strategy was used: Aging OR Senescence OR Aged OR Elderly OR “Healthy Aging” OR “Aging Well” OR “Healthy Ageing” AND “Amyloid beta-Peptides” OR “Amyloid beta Peptides” OR “Alzheimer beta-Protein” OR “Alzheimer’s ABP” OR “beta-Amyloid Protein” OR “Amyloid beta Protein” OR “Amyloid Protein A4” OR “beta Amyloid” OR “Amyloid AD-AP” OR “Amyloid” OR “Amyloid Substance” OR “Amyloid Fibril” OR β-amyloid OR amyloid-β OR “amyloid β-peptide” OR “amyloid-beta” AND “Histology” OR “Histocytochemistry” OR “Immunohistochemistry” OR “Immunolabeling Technique” OR “Immunolabeling Technic” OR “Immunogold Technique” OR “Immunohistocytochemistry” OR Positron-Emission Tomography OR “Positron Emission Tomography Imaging” OR “PET Scan” OR “PET Imaging” AND “Episodic Memory” OR “Autobiographical Memory” OR “Prospective Memory.” The key words were chosen even in the absence of a specific term (according to the MeSH) to prioritize sensitivity over the specified theme. In addition, we examined the reference lists in the retrieved studies.

**Selection criteria**

We included studies that investigated Aβ deposition in healthy aging and its relationship with decline in EM. We adopted the following inclusion criteria: (a) we investigated Aβ in the hippocampus in individuals with healthy aging and (b) we used the tasks to assess EM. We excluded studies that (a) used animal models, (b) did not assess the hippocampus, (c) evaluated another type of memory instead of episodic, and (d) were literature reviews.
Data extraction
For each study, data were extracted independently by two authors (GS and JS) using a structured form. The discrepancies were resolved by consulting a third author (NA) if needed. If there was insufficient information in the studies, the respective author was contacted. The following variables were extracted: (1) demographic and clinical characteristics (e.g., number of patients); (2) study design; (3) characteristics of the techniques; (4) task for assessing EM; and (5) main findings.

Quality assessment
We performed individual and comprehensive quality assessments for each study. The studies were also evaluated based on internal validity (i.e., selection bias or attrition bias) and construct validity (i.e., adequacy of the operational criteria used). In general, the quality and evidence of the studies were assessed based on three main measures, namely, (a) limitations (e.g., poorly designed strategies), (b) consistency of the results, and (c) accuracy (i.e., ability to generalize findings and provide sufficient data). A quality assessment was conducted using the PEDro scale and the Appraisal Tool for Cross-Sectional Studies (AXIS).

RESULTS
The initial search of the databases identified 517 studies. After screening the title, abstracts, key words, and article references, a total of 56 studies were in compliance with the inclusion criteria. Figure 1 presents the diagram flow and the details used to identify studies in our review.

---

**Figure 1.** Flowchart of the present study.
General characteristics of the studies
Table 1 presents the selected studies, which were published between 2010 and 2021. Thirty studies (53.6%) were published between 2010 and 2016, and the other 26 studies (46.4%) were published between 2017 and 2021. Regarding the sample size, the studies showed a variance between 45 and 2,908 participants, the majority (76.8%) being more than 100 participants.

A longitudinal study design was used in almost all of the selected studies (71.4%), whereas eight studies (28.6%) employed a cross-sectional design. Follow-up in these studies ranged between 6 months and 23 years. Diagnostic criteria also varied between studies, that is, 24 studies used the Mini-Mental State Examination (85.7%), 16 studies used the Clinical Dementia Rating (57.1%), 12 studies used the Geriatric Depression Scale (42.8%), and 5 studies used the Hospital Anxiety and Depression Scale (17.8%).

Techniques for investigating Aβ
We observed four types of techniques for investigating Aβ. The main technique used was positron emission tomography (PET), performed in 53 studies (94.6%). Three types of radioligands were used for the PET technique. Pittsburgh compound B was used in most of the studies (75%), while florbetapir F 18 and flutemetamol F 18 were used by a limited number of studies, i.e., nine (16%) and two (3.6%) studies, respectively. In addition, electrochemiluminescence techniques (in one study, 1.8%), CSF collection (in one study, 1.8%), and selected reaction monitoring (in one study, 1.8%) were also used.

Tasks used for the assessment of episodic memory
Most studies (67.9%) utilized between two and four different neuropsychological tests to assess EM. Approximately, 25 of these studies (44.6%) concentrated their assessments based on two types of tests. Predominantly, most of them used neuropsychological measures, such as California Verbal Learning Test (CVLT; 35.7%), Rey Complex Figure Test (RCFT; 19.6%), Logical Memory Recall (17.8%), Rey Auditory Verbal Learning Test (16%), and the Wechsler Memory Scale-Revised (12.5%). Five studies did not specify the tests used in the neuropsychological assessment.

Main findings
The main findings are presented in Table 1. The scope of the selected studies included heterogeneous objectives. Nevertheless, all the studies evaluated common aspects of Aβ deposition in cortical structures, especially in the hippocampus, and its relationship with EM. Hence, the results have specificities. In general, most studies (83.9%) indicated that the increase in Aβ was related to worse performance in EM tests. One of these studies even indicated that Aβ deposition in women makes them more vulnerable to declines in EM. In contrast, some studies (16.1%) indicated that the increase in Aβ did not correspond to differences in EM.

Quality assessment
Based on the PEDro scale, which comprised 11 items, 56 studies obtained an overall average of 5.7 points, approaching the score considered by the moderate- to high-quality instrument (≥6.0 points — moderate to high quality). Overall, 53.6% were considered of moderate quality (4.0–5.0 points) and the other 46.4% were of moderate to high quality (6.0–9.0 points). Based on the AXIS, the overall average was 16.2 points on a scale ranging from 0 to 20 points. Overall, 28.6% (16 studies) scored from 0 to 15 points and the other 71.4% (40 studies) reached ≥15.0 points, showing a lower risk of bias and higher quality of the studies. Both the assessment tools showed good results with regard to the quality of the selected studies.

The discrepancies between the evaluations within these two scales may be related to the objective for which each one was designed. While AXIS provides an evaluation of more general items, PEDro provides an assessment for more specific aspects in clinical trials, so the lowest PEDro score, especially in items related to blinding, can signal possible biases, like exaggerating or reporting fewer symptoms. These biases can induce different rates of, for example, co-intervention, friction, and placebo effect. Furthermore, our results suggest that future studies should exercise caution in the definition and methodological execution, so that the studies are in accordance with the guidelines of the designs to which they are proposed.

DISCUSSION
There are significant increases in research aimed at identifying diagnostic and prognostic biomarkers of AD. The updated AD research structure proposed by the National Institute on Aging and Alzheimer’s Association working group defines AD as a biological construct, and the research focused on the diagnosis of AD in those who are alive using biomarkers that cover the presymptomatic and symptomatic stages of the disease. Biomarkers are grouped into those of Aβ deposition, pathological tau, and neurodegeneration. Although it is possible that Aβ plaques and neurofibrillary tau deposits are not the cause of AD pathogenesis, these abnormal protein deposits define AD as a unique neurodegenerative disease among various diseases that can lead to dementia.
Table 1. Characteristics of the selected studies.

| Authors            | Sample | Aβ technique       | Others techniques | Regions of interest                          | EM task           | Main findings                                                                 | PEDro | AXIS |
|--------------------|--------|--------------------|-------------------|----------------------------------------------|-------------------|-------------------------------------------------------------------------------|-------|------|
| Chételat et al.58  | 93     | PIB-PET            | N/A               | Gray matter, white matter, and CSF           | CVLT-II And RCFT  | EM involvement is related to Aβ deposition, especially in the temporal neocortex, and regardless of hippocampal atrophy | 4     | 15   |
| Lim et al.59       | 141    | PIB-PET            | Blood exam        | Cerebellum                                   | CVLT-II and PAL   | High Aβ showed significantly greater decline in verbal and visual EM at 18 months | 5     | 15   |
| Marchant et al.60  | 54     | PIB-PET            | MRI and FLAIR     | CSF, WMH, frontal, parietal, and temporal cortex, posterior cingulate, and precuneus | CVLT and MAS      | Aβ did not explain changes in EM                                               | 5     | 16   |
| Perrotin et al.61  | 48     | PIB-PET            | MRI               | Medial PFC/ACC, precuneus/ PCC/ICC, and temporal lobe | CVLT-II and WMS-R | High Aβ performed worse than low Aβ just on the EM measure test CVLT          | 5     | 15   |
| Rodrigue et al.62  | 137    | F-florbetapir PET  | Blood exam        | −                                             | HVLT and CANTAB   | Aβ subgroup has no significant association with EM                             | 5     | 16   |
| Adamczuk et al.63  | 64     | F-flutemetamol PET | MRI               | Frontal, parietal, anterior cingulate, precuneus/ posterior cingulate, and lateral temporal | BNT, AVF, and RPM | Aβ and EM were negatively correlated only in the BDNF group of met +ve/APOE ε 4 +ve | 5     | 14   |
| Doré et al.64      | 133    | PIB-PET            | MRI               | Gray matter, white matter, CSF, and cerebellum | CVLT-II and LMT-II | No significant differences in EM between the Aβ- and Aβ+ groups. There was a significant reduction in the precuneus and hippocampus | 5     | 13   |
| Ellis et al.65     | 178    | PIB-PET            | Blood exam        | Frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate | CVLT-II, LMR, and RCFT | High Aβ showed greater decline in EM                                           | 5     | 14   |
| Hedden et al.66    | 168    | PIB-PET            | MRI and FLAIR     | Frontal, lateral, parietal, temporal, and retrosplenial cortices | FNAME, STSRT, and MCT | Aβ burden and WMH had distinct cognitive profiles. Aβ was associated with a decline in EM | 5     | 14   |

Continue...
### Table 1. Characteristics of the selected studies.

| Authors            | Sample | Aβ technique | Others techniques | Regions of interest                                                                 | EM task                        | Main findings                                                                 | PEDro | AXIS |
|--------------------|--------|--------------|-------------------|--------------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------|-------|------|
| Lim et al.⁶⁷       | 234    | PIB-PET      | Blood exam        | Cerebellar cortex, frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate | CVLT-II and RCFT             | No differences were observed between HC high and low Aβ groups                  | 4     | 15   |
| Sperling et al.⁶⁸  | 78     | Florbetapir F 18 PET | MRI           | Grey matter, frontal, temporal, parietal cortices, anterior cingulate, and posterior cingulate | WLM-I, WLM-D, and DSS         | The highest SUVr correlated with the lowest immediate memory                    | 8     | 16   |
| Wirth et al.⁶⁹     | 38     | PIB-PET      | FDG-PET and MRI  | Frontal, temporal, parietal, and anterior/ posterior cingulate                         | LMR and VRT                   | PiB positivity was associated with nonmemory decline                           | 3     | 14   |
| Lim et al.²⁰       | 225    | PIB-PET      | Blood exam        | Cerebellar cortex                                                                     | CVLT-II                       | High Aβ HC and MCI groups showed moderate decline in EM                         | 7     | 16   |
| Lim et al.²¹       | 413    | PIB-PET      | Blood exam        | Cerebellar cortex                                                                     | LMR, CVLT-II, RCFT, and COCLT | Aβ+ showed greater decline on the verbal EM and visual EM                       | 7     | 16   |
| Ossenkoppele et al.²²| 81    | PIB-PET      | FDG-PET and MRI  | Gray matter, posterior cingulate cortex, bilateral angular gyri, and bilateral inferior temporal gyri | CVLT and VRT                  | Aβ was associated with higher metabolic activity and lower visual episodic memory scores | 5     | 15   |
| Villeneuve et al.⁹  | 67     | PIB-PET      | MRI               | Right frontal, parietal, temporal, occipital, and precuneus                           | MAS                           | High Aβ was associated with cortical thinning and lower performance of EM       | 5     | 16   |
| Amariglio et al.²³  | 257    | PIB-PET      | FDG-PET and MRI  | Hippocampal volume                                                                   | FNAME, STSRT, and MCT         | Aβ and ND biomarkers predict biggest changes in EM                               | 8     | 16   |
| Aschenbrenner et al.²⁴| 238   | PIB-PET      | Cerebrospinal fluid assessment | Orbitofrontal, parietal, frontal, and temporal                                           | SRT                           | EM was not correlated with levels of Aβ                                         | 5     | 16   |

Continue...
Table 1. Characteristics of the selected studies.

| Authors            | Sample | Aβ technique | Others techniques | Regions of interest | EM task | Main findings                                                                 | PEDro | AXIS |
|--------------------|--------|--------------|-------------------|--------------------|---------|------------------------------------------------------------------------------|-------|------|
| Lim et al.         | 227    | PIB-PET      | MRI               | Gray matter, white matter, cerebrospinal fluid, and hippocampus | OCL     | Aβ+ CN and MCI groups showed decline on the EM measures                      | 6     | 15   |
| Lim et al.         | 333    | PIB-PET      | Blood exam        | Cerebellar cortex  | LMR, CVLT-II, RCFT, and COCLT | Aβ+ ε4+ individuals showed cognitive decline across all domains. Aβ+ ε4− individuals showed faster decline only in verbal EM | 8     | 17   |
| Mander et al.      | 26     | PIB-PET      | fMRI and EEG      | Hippocampus and mPFC | TWPT    | Aβ impairs sleep and has indirect implications for EM decline                | 8     | 18   |
| Mattsson et al.    | 743    | Florbetapir PET | FDG-PET and MRI  | Gray matter, LMR and AVLT | Aβ+ was associated with lower EM scores | 4     | 16   |
| Pietrzak et al.    | 333    | PIB-PET      | –                 | CVLT and LMR       | High Aβ was associated with a subtle decrease in EM | 8     | 16   |
| Racine et al.      | 175    | Electrochemiluminescence | MRI and FLAIR | RAVLT and WMS-RLM | High levels of Aβ and higher rates of decline in EM tests | 4     | 18   |
| Wang et al.        | 188    | CSF collection | MRI               | N/A                | Reduced CSF Aβ42 was related to poorer performance on EM | 3     | 16   |
| Wang et al.        | 263    | PIB-PET      | Blood exam        | LMRD and WLRD      | For asymptomatic carriers, Aβ burden was predictive of longitudinal decline in EM | 8     | 15   |
| Bischof et al.     | 147    | Florbetapir PET | –                 | HVLT and CANTAB    | Higher Aβ may have an influence on EM, especially between 30 and 55 years of age | 7     | 16   |
| Lim et al.         | 423    | PIB-PET      | Blood exam        | Cerebellar cortex  | CVLT, LMR, and RCFT | Significantly increased decline in EM in Aβ+ APOE ε4 carriers | 7     | 17   |

Continue...
Table 1. Characteristics of the selected studies.

| Authors                | Sample | Aβ technique | Others techniques | Regions of interest | EM task                          | Main findings                                                                 | PEDro | AXIS |
|------------------------|--------|--------------|-------------------|---------------------|---------------------------------|--------------------------------------------------------------------------------|-------|------|
| Mielke et al.84        | 465    | PIB-PET      | –                 | –                   | AVLT, WMS-RLM, WMS-RVR, and CogState | High Aβ was not associated with changes in EM                                   | 5     | 16   |
| Song et al.85          | 82     | F18-AV-45-florbetapir PET | MRI and fMRI     | –                   | HVLT and CANTAB                 | Aβ had no effects or interaction in EM                                         | 4     | 14   |
| Ayton et al.86         | 117    | PIB-PET      | –                 | –                   | CVLT and RCFT                   | Aβ pathology and higher levels of quantitative susceptibility of the hippocampus predicted accelerated deterioration in EM | 6     | 17   |
| Boots et al.87         | 140    | PIB-PET      | –                 | –                   | RAVLT                           | BDNF was associated with a decline in EM and was exacerbated by a greater Aβ load | 6     | 17   |
| Farrell et al.88       | 174    | F-florbetapir PET | –                 | –                   | –                               | Aβ+ and the increase in baseline SUVR predicted an increasing decline in EM     | 7     | 16   |
| Lim et al.89           | 989    | PIB-PET      | Blood exam and MRI| Hippocampus volume | CVLT-II, LMR, and RCFT          | APOEε4 homozygotes (ε4/ε4) showed significantly worse EM and higher Aβ levels than heterozygous ε4 | 5     | 14   |
| Lim et al.90           | 446    | PIB-PET      | Blood exam        | Hippocampus volume | LMR, CVLT-II, and RCFT          | Aβ- Val and Aβ+ Val homozygotes showed a decline in EM                           | 4     | 17   |
| Pietrzak et al.91      | 416    | PIB-PET      | MRI               | Plasmatic cortisol   | CVLT-II, LMR, and RCFT          | Older Aβ+ adults experienced a faster decline in EM                            | 3     | 16   |
| Vogel et al.92         | 136    | PIB-PET      | –                 | –                   | N/A                             | Decline in EM was observed only when cognitive decline and Aβ were present     | 7     | 17   |
| van Bergen et al.93    | 116    | Flutemetamol PET | MRI               | –                   | MMSE and VLMT                   | Local correlation between iron and β-amyloid is related to levels of cognitive performance | 5     | 18   |
| Bilgel et al.94        | 171    | PIB-PET      | MRI               | Hippocampus         | CVLT and BVRT                   | Amyloidosis or hippocampal atrophy had longitudinal declines in EM verbal and learning | 3     | 17   |

Continue...
### Table 1. Characteristics of the selected studies.

| Authors         | Sample | Aβ technique | Others techniques | Regions of interest | EM task          | Main findings                                                                 | PEDro | AXIS |
|-----------------|--------|--------------|-------------------|---------------------|------------------|-------------------------------------------------------------------------------|-------|------|
| Farrell et al.  | 126    | Florbetapir PET | MRI               | Hippocampal and cortical volume | HVLR and CANTAB | Decline in EM and increase in Aβ accumulation                                  | 7     | 18   |
| Jansen et al.   | 2,908  | PIB-PET      | –                 | –                   | VLVT             | Aβ positivity was associated with low memory                                   | 6     | 17   |
| Leal et al.     | 71     | PIB-PET      | –                 | –                   | WMS - II and CVLT | Higher levels of Aβ are associated with the decline of EM                      | 5     | 16   |
| Lim et al.      | 447    | PIB-PET      | MRI               | –                   | RAVLT            | Worsens in EM of Aβ+ than Aβ− and may exacerbate with age                      | 5     | 18   |
| Mecca et al.    | 45     | PIB-PET      | MRI               | Gray matter         | N/A              | In middle-aged individuals, Aβ load does not affect EM performance            | 6     | 18   |
| Ko et al.       | 762    | PIB-PET      | –                 | –                   | RAVLT and ADAS-Cog | EM was a predictor for Aβ positivity                                           | 6     | 17   |
| Pothier et al.  | 65     | F-florbetapir PET | –                 | –                   | FCSRT            | Significant difference for EM over time, with better performance in Aβ− compared with Aβ+ | 8     | 19   |
| Rabin et al.    | 253    | PIB-PET      | MRI               | Fornix              | WMS-RLM, FCSRT, and STSRT | Elevated Aβ load has been associated with a faster decline in EM over time | 4     | 17   |
| Rahayel et al.  | 104    | PIB-PET      | MRI               | –                   | WMS - III and RAVLT | Higher Aβ had worse episodic memory                                            | 5     | 17   |
| Yu et al.       | 148    | SRM          | –                 | –                   | –                | Aβ is unrelated with decline in EM                                              | 8     | 19   |
| Dupont et al.   | 104    | PIB-PET      | MRI               | WMHs                | LMT -II          | Deposition Aβ predicts weaker EM performance                                   | 8     | 18   |
| Joannette et al.| 104    | PIB-PET      | MRI               | –                   | RAVLT            | EM performance is associated with Aβ load                                     | 6     | 18   |
| Lim et al.      | 213    | PIB-PET      | Blood exam        | –                   | CVLT and RAVLT   | Aβ is related to the decline of EM                                             | 7     | 16   |
| Lindbergh et al.| 149    | Florbetapir PET | Gray matter       | –                   | RAVLT and RCFT | Women with high Aβ are more vulnerable to declining EM than men               | 6     | 18   |

Continue...
The preclinical imaging methods used by diagnostic of amyloid accumulation and neurodegeneration (i.e., imaging PET) and biofluids (CSF and blood plasma) are very expensive and difficult to use in research. Therefore, the attention of researchers is directed to the search for predictors of the disease, which indirectly reflect the functional activity of the structures involved in the pathological process.

With regard to the prognostic value, the most relevant studies sought to identify biomarkers at early stages of AD pathogenesis, particularly the studies involving groups of healthy elderly individuals, characterized by the accumulation of cerebral amyloid plaques in the absence of clinical symptoms of mild cognitive impairment (MCI) or dementia. The hippocampus is a key brain region that processes EM and is a primary structure that is susceptible to the accumulation of amyloid plaques. However, some structures such as the entorhinal cortex and the cingulate gyrus are also relevant to the matter. Currently, some studies aimed at studying the relationship of minimal cognitive impairment, including the decline of EM, in different groups of subjects such as those with AD symptoms and/or MCI and the elderly with preservation of cognitive functions. The drawback is that the methods and procedures used to investigate EM vary and do not always accurately reflect EM. It is also important to mention that visual processing is one of the main biomarkers for cognitive decline.

An episode can be classified as “what” happens “where,” with contextual information (temporal “when,” or circumstantial “which”) that fosters contextual and behavioral criteria. As follows, the hippocampal formation is necessary for learning and memory, particularly for spatial components. The trigger between pyramidal neurons in the CA1 and CA3 regions is one of the main biomarkers for cognitive decline.

### Table 1. Characteristics of the selected studies.

| Authors                        | Sample | Aβ technique | Others techniques | Regions of interest | EM task   | Main findings                                                                 | PE директор | AXIS |
|--------------------------------|--------|--------------|-------------------|--------------------|-----------|------------------------------------------------------------------------------|--------------|------|
| Squarzoni et al.               | 108    | PIB-PET      | MRI and FDG-PET   | Hippocampal subregions | AVLT and SCPT | Aβ load and poorer memory performance were detected only in stages +               | 6            | 16   |
| Busatto Filho et al.           | 124    | PIB-PET      | MRI               | Hippocampal subregions | AVLT and SCPT | Subicular volumes were inversely correlated with the degree of Aβ deposition. Verbal EM scores were significantly lower in both (N)+ groups | 5            | 15   |
| Han et al.                     | 154    | PIB-PET      | MRI               | VL and WS          | SENAS     | Aβ influence retention in EM change                                             | 6            | 19   |

6-7TSRT: 6-Trial Selective Reminding Test; Aβ: amyloid-β; AD: Alzheimer’s disease; ADAS-Cog: Alzheimer’s Disease Assessment Scale–Cognitive Subscale; APOE: apolipoprotein E; AIF: Animal Verbal Fluency Test; AVLT: Auditory Verbal Learning Test; BDNF: brain-derived neurotrophic factor; BNT: Boston Naming Test; BVRT: Benton Visual Retention Test; CAA: cerebral amyloid angiopathy; CANTAB: Cambridge Neuropsychological Test Automated Battery; CSF: cerebrospinal fluid; COBT: Cogstate One Back Task; COCOT: Cogstate One Card Learning task; CVLT-II: California Verbal Learning Test, second edition; DMST: Delayed Matching-to-Sample Task; DTI: diffusion tensor imaging; EEG: electroencephalogram; ELISA: enzyme-linked immunosorbent assay; EM: episodic memory; FCSRT: Free and Cued Selective Reminding Test; FDG: fluorodeoxyglucose; FLAIR: fluid attenuation inversion recovery; fMRI: functional magnetic resonance imaging; FNAME: Face-Name Associative Memory Exam; FRET: Face–Name Experimental Task; FSRT: Free and Selective Reminding Test; HUL: Hopkins Verbal Learning Immediate Recall; HUT: Hopkins Verbal Learning Task; PIB-PET: Pittsburgh compound B positron emission tomography; IA: immunosorbent assay; LMT-II: Logical Memory Test, second edition; LMR: Logical Memory Recall; MAC-O: Memory Complaint Questionnaire; MMS: Memory Assessment Scale; MBT: Memory Binding Test; MMSE: Mini Mental State Examination; MPAGE: magnetization-prepared rapid gradient echo; MRI: magnetic resonance imaging; MCT: Memory Capacity Test; mPFC: medial prefrontal cortex; MT: magnetic resonance; MTL: medial temporal lobe; N/A: no data available; OCL: One Card Learning; PALS: paired-associate learning; P-tau: tau pathology; PAVLT: Rey Auditory Verbal Learning Test; RCOFT: Rey Complex Figure Test; ROCF: Rey-Osterrieth complex figure; RPM: Raven’s Progressive Matrices; SCC: subjective cognitive concerns; SCPT: Short Cognitive Performance Test; SENAS: Spanish and English Neuropsychological Assessment Scale; SMD: subjective memory decline; SRT: Selective Reminding Test; STSRT: Six-Trial Selective Reminding Test; SUVR: neocortical standardized uptake value ratio; TMADA: TaqMan allelic discrimination assay; TWPT: the word-pairs task; WAPS: Visual Paired Associates Total Score; VL: vascular load; VRM: verbal recognition memory; WRT: Visual Reproduction Test; WLT: Verbal Word Learning Test; WMS: Wechsler Adult Intelligence Scale; WLM-V: Wechsler Logical Memory–Delayed Recall; WM: working memory; WMS-R: Wechsler Memory Scale-Revised Logical Memory; WMS-RVR II: Wechsler Memory Scale-Revised Visual Reproductions II; WLIRO: Word List Immediate Recall and Delayed Recall; WLM-I: Wechsler Memory Scale–Revised Logical Memory Immediate Recall and Delayed Recall; MCI: mild cognitive impairment; Dementia and other cognitive disorders; CAA: cerebral amyloid angiopathy; AVF: Animal Visual Fluency Test; APOE: apolipoprotein E; ADAS-Cog: Alzheimer’s Disease Assessment Scale–Cognitive Subscale; AD: Alzheimer’s disease; CINT: Cerebrospinal fluid c-kinase. 

38,39 An episode can be classified as “what” happens “where,” with contextual information (temporal “when,” or circumstantial “which”) that fosters contextual and behavioral criteria. As follows, the hippocampal formation is necessary for learning and memory, particularly for spatial components. The trigger between pyramidal neurons in the CA1 and CA3 regions is clearly correlated with the location of an individual.
The ablation of the hippocampal formation, in turn, impairs spatial navigation ability.

The tests such as CVLT and RCFT have considerable clinical predictive value and reliability and are widely used for the clinical assessment of EM.\textsuperscript{16,17} However, classic neuropsychological tests are limited to evaluating the recall of focal elements, such as lists of images or words, freely or with the use of cues.\textsuperscript{18,19} Thus, they are more associated with semantic or verbal processes than episodic processes, and they do not consider contextual elements.\textsuperscript{19} Most studies that were discussed in this review attempted to circumvent this hindrance by employing at least two types of classic neuropsychological tests to assess EM. However, the set of tests that are used by these studies may not provide an assessment that fully integrates “what,” “where,” and “when” components that are essential for predicting real memory performance in everyday life.\textsuperscript{19,20} Additionally, using a battery of tests can be tiring for respondents, especially for the elderly people. The Treasure Hunt task\textsuperscript{20} is proposed to investigate three components (i.e., what, where, and when) and be useful for further studies. This task was developed by Cheke\textsuperscript{20} and is proposed to assess the memory of object information (“what”), location information (“where”), and temporal order information (“when”) within the same testing paradigm. This is important because it integrates all three features into a classic what–where–when framework. This task can also identify the extent and pattern of EM deficits that might be present in several diseases. Although no normative data have been published for the Treasure Hunt task, its application can still be useful. It is difficult to identify whether there is a specific deficit of EM, and the Treasure Hunt task can be an important alternative or complement to the existing assessment tools.

The divergence between age and cognitive functioning may be grounded in the medial temporal lobe (MTL). The MTL, comprising interconnected structures of the hippocampus, dentate gyrus, peri- and entorhinal cortices, and parahippocampal gyrus, undergoes a prolonged period of postnatal development in humans, nonhuman primates, and rodents, with different maturation timelines. The MTL also impacts learning and memory functions differently in time.\textsuperscript{40} These areas have functions in general mnemonic processes, specifically EM in humans and rats. It has been suggested that the function of the hippocampus is to integrate details of events that have been experienced, including spatial locations, together to gather episodic memories.\textsuperscript{31}

EM is a multisensory neurocognitive process of linking many elements. The unification of many elements in an episode occurs because of the long-term potentiation in the MTL and the activity of hippocampal neurons in the theta phase.\textsuperscript{52,41} Studies have demonstrated that theta cycles determined the process packaging of principal cell spiking into functional ensembles \textit{via} the provision of discrete windows in which incoming streams of information from different systems are processed.\textsuperscript{44,45}

In addition, there is ample evidence that the N-methyl-D-aspartate glutamatergic receptor has a fundamental function in inducing synaptic plasticity and memory formation for various tasks involving aversive conditioning,\textsuperscript{47} training of spatial memory,\textsuperscript{48} nonspatial, and nonaversive tasks\textsuperscript{49} in rodents.\textsuperscript{46} These studies provided evidence that the deposition of neocortical and hippocampal Aβ in elderly people with normal cognitive aging is associated with functional changes in EM.\textsuperscript{50} In general, aging is associated with a reduced ability to modulate MTL activity, that is, with aging, the hippocampus shows a decrease in activation, and the entorhinal cortex decreases inhibition during an EM task. In addition, among elderly individuals, Aβ deposition was associated with a reduction in the entorhinal cortex regions associated with standard network functioning.\textsuperscript{15,9}

It is strongly suggested that in elderly individuals with a high concentration of Aβ, the preclinical processes of AD have begun despite normal cognitive functioning, even in the absence of changes in clinical findings. It is important to mention that this can be detected over a short period of time through the use of neuropsychological measures.\textsuperscript{31} Age and Aβ deposition contribute to a collapse of the network between the hippocampus and regions of the neocortex, suggesting the declines in EM.

Aging-related dementia usually begins gradually, with hippocampal atrophy manifesting several years after the onset of clinical symptoms. Aβ deposition is a part of the pathophysiology of AD, and therefore Aβ is more focused as a biomarker of AD. It is known that the role of Aβ in neurodegeneration culminates in a cascade of harmful events such as dementia and AD. However, this review noted that even in the presence of cognitive aging, Aβ can be detected in some individuals. The factors or issues that make individuals to be at risk of developing AD are still unclear.\textsuperscript{51,52}

One key to improving our understanding of the relationship between normal aging and initial stages of AD is related to neuroplasticity and cognitive decline that results from a lack of a compensatory response to the accumulation of Aβ. The leading genetic risk factor for AD, namely, apolipoprotein ε4, is related to neural...
plasticity. The high levels of cognitive reserves are associated with the level of education and socioeconomic status of an individual and delay in the diagnosis of AD53. Individuals with greater cognitive reserves can maintain cognitive function in the face of the higher levels of cerebral Aβ deposition in the hippocampus during aging54. Weak correlations between the levels of Aβ deposition and cognitive function suggest that other mechanisms, such as functional compensation, influence cognitive ability. The views that cognitive function can be maintained during aging by compensatory cognitive processes and that this decline is seen when a person is no longer able to compensate for a decrease in the function of primary brain structures and circuits are well supported in the contemporary research55,56.

High-performing elderly adults are quite interesting in this regard. High-performing elderly individuals exhibit global preservation of the cerebral cortex, especially the anterior cingulate gyrus, and the volume of the hippocampus is higher than in people of normal age. The histological analyses of this group also revealed lower amyloid burden and lower neurofibrillary tangles compared with cognitively normal elderly controls. Thus, further studies of high-performing older adults are likely to provide additional insights in the role of amyloid deposition in the hippocampus during the aging process57.

Despite the strengths of this review, it has some limitations. First, this review included studies that involved age ranges, which created challenges in interpreting these results (e.g., age is directly associated with amyloid deposition). Second, several studies used tests that assessed only specific parts of EM (e.g., delayed recall), thus raising the need to use extensive neuropsychological assessments or tests, such as the Treasure Hunt task, that encompass all three main aspects of EM. Third, the analysis of various brain regions raises the need to define possible neural networks that are responsible for EM processing.

Finally, we noted the need for further research in this area. It is necessary to investigate this concept in order to understand the prodromal symptoms of AD and the emergence of new practices and techniques that can identify and map Aβ deposition during healthy aging.

Authors’ contributions. JS: conceptualization, literature review, writing – original draft, and writing – review & editing. GS: conceptualization, literature review, writing – original draft, and writing – review. NA: conceptualization and writing – original draft. IS: conceptualization, writing – review & edition. NS: project administration, supervision, and writing – review & editing. TF: project administration, supervision, and writing – review & editing.

REFERENCES

1. Huljers W, Morrow EC, Wigman SE, Ward AM, Vannin P, McLaren DG, et al. Amyloid deposition is linked to aberrant entorhinal activity among cognitively normal older adults. J Neurosci. 2014;34(4):5200-10. https://doi.org/10.1523/JNEUROSCI.3579-13.2014

2. Mormino EC, Smijic A, Hayenga AO, Onami SH, Greicius MD, Rabinovici GD, et al. Relationships between β-amyloid and functional connectivity in different components of the default mode network in aging. Cereb Cortex N Y N 1991. 2011;21(10):2399-407. https://doi.org/10.1093/cercor/bhr025.

3. Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL, et al. Episodic memory loss is related to hippocampal-mediated β-amyloid deposition in elderly subjects. Brain. 2009;132(Pt 5):1310-23. https://doi.org/10.1093/brain/awm320.

4. Tulving E. Episodic memory: from mind to brain. Annu Rev Psychol. 2002;53:1-25. https://doi.org/10.1146/annurev.psych.53.100901.135114.

5. Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. Alzheimer’s disease neuroimaging initiative what is normal in normal aging? Effects of aging, amyloid and Alzheimer’s disease on the cerebral cortex and the hippocampus. Prog Neurobiol. 2014;117:20-40. https://doi.org/10.1016/j.pneurobio.2014.02.004.

6. Blennow K, Zetterberg H. Biomarkers for Alzheimer’s disease: current status and prospects for the future. J Intern Med. 2018;284(6):643-63. https://doi.org/10.1111/jim.12816.

7. Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer’s disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207-16. https://doi.org/10.1016/S1474-4422(12)70291-0.

8. Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade. Lancet Neurol. 2010;9(1):119-28. https://doi.org/10.1016/S1474-4422(09)70299-6.

9. Villeneuve S, Reed BR, Wirth M, Haase CM, Madison CM, Ayakta N, et al. Cortical thickness mediates the effect of β-amyloid on episodic memory. Neurology. 2014;82(9):761-7. https://doi.org/10.1212/WNL.000000000000170.

10. Davatzikos C, Xu F, An Y, Fan Y, Resnick SM. Longitudinal progression of Alzheimer’s-like patterns of atrophy in normal older adults: the SPARE-AD index. Brain J Neurol. 2009;132(Pt 8):2026-35. https://doi.org/10.1093/brain/awp091.

11. Burgmans S, van Boxtel MP, Vuurman EF, Smeets F, Gronenschild EH, Uylings HB, et al. The prevalence of cortical gray matter atrophy may be overestimated in the healthy aging brain. Neuropsychology. 2009;23(5):541-50. https://doi.org/10.1037/a0016161.

12. Sliwinski M, Buschke H. Cross-sectional and longitudinal relationships among age, cognition, and processing speed. Psychol Aging. 1999;14(1):18-33. https://doi.org/10.1037/0882-7974.14.1.18.

13. Nyberg L, Salami A, Andersson M, Eriksson J, Kalpouzos G, Kauppi K, et al. Longitudinal evidence for diminished frontal cortex function in aging. Proc Natl Acad Sci. 2010;107(52):22682-6. https://doi.org/10.1073/pnas.1012651108.

14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100. https://doi.org/10.1371/journal.pmed.1000100.

15. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097.

16. Elwood RW. The Wechsler Memory Scale-Revised: psychometric characteristics and clinical application. Neuropsychol Rev. 1991;1(2):179-201. https://doi.org/10.1007/BF01109053.
17. Woods SP, Delis DC, Scott JC, Kramer JH, Holchinack JA. The California Verbal Learning Test — second edition: test-retest reliability, practice effects, and reliable change indices for the standard and alternate forms. Arch Clin Neuropsychol. 2006;21(5):413-20. https://doi.org/10.1016/j.acn.2006.06.002

18. Strauss E, Sherman EM, Spreen O. A compendium of neuropsychological tests: Administration, norms, and commentary. 3rd ed. New York: Oxford University Press; 2006.

19. Cheke LG, Clayton NS. Do different tests of episodic memory produce consistent results in human adults? Learn Mem. 2013;20(8):491-8. https://doi.org/10.1101/lm.305022.113

20. Cheke LG, Worrall-Curiale and memory strategies in healthy aging. Learn Mem. 2016;23(3):121-6. https://doi.org/10.1101/lm.04840.140

21. Vannini P, Heedden T, Becker JA, Sullivan C, Putcha D, Rentz D, et al. Age and amyloid-related alterations in default network habituation to stimulus repetition. Neurobiol Aging. 2012;33(3):1292-201. https://doi.org/10.1016/j.neurobiolaging.2011.01.003

22. Marks SM, Lockhart SN, Baker SL, Jagust WJ. Tau and beta-amyloid are associated with medial temporal lobe structure, function, and memory encoding in normal aging. J Neuropsychiatry Clin Neurosci. 2017;29(2):319-22. https://doi.org/10.1176/appi.neuropsychiatry.16040066

23. Lindberger CA, Casaletto KB, Staffaroni AM, Joie RL, Iaccarino L, Edwards LM. The cognitive neuroscience of ageing. Nat Rev Neurosci. 2011;12(9):572-82. https://doi.org/10.1038/nrn3077

24. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a selective visual deficit of higher-level dorsal pathway. J Alzheimers Dis. 2016;53(2):661-76. https://doi.org/10.3233/JAD-201509316-X

25. Sawyer JJ, Yaffe K, Martinez FA, Mehta H, Luchsinger JA, Kukull WA, et al. Age and amyloid-related alterations in default network habituation to stimulus repetition. Neurobiol Aging. 2012;33(5):1006.e25-36. https://doi.org/10.1016/j.neurobiolaging.2011.04.001

26. Hróbjartsson A, Boutron I. Blinding in randomized clinical trials: implications for the design and interpretation of trials in which blinding is not feasible. Stat Med. 2011;30(24):2880-92. https://doi.org/10.1002/j.1097-0258.2011.01653.x

27. Sivak JM. The aging eye: common degenerative mechanisms between the mechanisms of the brain and retinal disease. Invest Ophthalmol Vis Sci. 2013;54(1):871-90. https://doi.org/10.1167/iovs.12-10827

28. Mahler OG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDRO Scale for rating quality of randomized controlled trials. Phys Ther. 2003;83(8):713-21. https://doi.org/10.1093/ptj/83.8.713

29. Hróbjartsson A, Boutron I. Blinding in randomized clinical trials: implications for the design and interpretation of trials in which blinding is not feasible. Stat Med. 2011;30(24):2880-92. https://doi.org/10.1002/j.1097-0258.2011.01653.x

30. Moschos MM, Markopoulo I, Chatziralli I, Rouvas A, Papageorgiou SG, Ladas I, et al. Stereotactic surgery for visual field defects: a systematic review of the literature. J Neurosurg. 2012;116(7):1267-75. https://doi.org/10.3171/2012.5.JNS11366

31. Fernandes TM, Andrade SM, Andrade MJ, Nogueira RM, Santos NA. Effect of age on visual acuity and contrast sensitivity in tobacco use disorder. Psychiatry Res. 2019;271:60-7. https://doi.org/10.1016/j.psychres.2020.113357

32. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDRO Scale for rating quality of randomized controlled trials. Phys Ther. 2003;83(8):713-21. https://doi.org/10.1093/ptj/83.8.713

33. Baker KB, Kim JJ. Effects of stress and hippocampal NMDA receptor antagonism on recognition memory in rats. Learn Mem Cold Spring Harb N Y. 2002;9(2):58-65. https://doi.org/10.1101/lm.4758.1

34. de Chastelaine M, Mattson JT, Wang TH, Donley BE, Rugg MD. The relationships between age, associative memory performance, and the neural correlates of successful associative memory encoding. Neurobiol Aging. 2016;42:163-76. https://doi.org/10.1016/j.neurobiolaging.2016.03.015

35. Lim YY, Pietrzak RH, Ellis KA, Jaeger J, Harrington K, Ashwood T, et al. Rapid decline in episodic memory in healthy older adults with high amyloid burden J Alzheimers Dis. 2013;39(3):675-9. https://doi.org/10.3233/JAD-2012-121516

36. Mattsson N, Insel PS, Aisen PS, Jagust W, Mackin S, Weiner M. Brain structure and function as mediators of the effects of amyloid on episodic memory. Neurology. 2013;81(11):1136-44. https://doi.org/10.1212/WNL.0b013e31826e9ae6

37. Stern Y. Cognitive reserve in ageing and Alzheimer’s disease. Lancet Neurol. 2012;11(11):1006-12. https://doi.org/10.1016/S1474-4422(12)70191-6

38. EclipSE Collaborative Members, Brayne C, Ince PG, Keage HAD, McKeith IG, Matthews FE, et al. Education, the brain and dementia: neuroprotection vs. compensation. Brain. 2014;137(Pt 8):2120-6. https://doi.org/10.1093/brain/awt185

39. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage. 2002;17(3):1394-402. https://doi.org/10.1016/nimg.2002.12.080

40. Grady C. The cognitive neuroscience of aging. Nat Rev Neurosci. 2012;13(7):491-506. https://doi.org/10.1038/nrn3256

41. Borell BV, Carusco KC, Studart-Neto A, Nitrin R, Caramelli P, Costa JD. Operationalized definition of older adults with high cognitive performance. Dement Neuropsychol. 2018;12(3):221-7. https://doi.org/10.1016/j.dnep.2018.01.007

42. Cheletel G, Villemagne VL, Pike KE, Ellis KA, Bourgeat P, Jones G, et al. Independent contribution of temporal beta-amyloid deposition to memory decline in the pre-dementia phase of Alzheimer’s disease. Brain. 2011;134(Pt 3):798-807. https://doi.org/10.1093/brain/awq383

43.Lim YY, Ellis KA, Pietrzak RH, Ames D, Darby D, Harrington K, et al. Smaller effect of amyloid than APOE genotype on cognitive decline in healthy older adults. Neurobiology. 2012;79(16):1645-52. https://doi.org/10.1016/j.neurobiolaging.2011.10.001
99. Mecca AP, Barcelos NM, Wang S, Brück A, Nabulsi N, Planeta-Wilson B, et al. Cortical β-amyloid burden, gray matter, and memory in adults at varying APOE ε4 risk for Alzheimer’s disease. Neurobiol Aging. 2018;61:207-14. https://doi.org/10.1016/j.neurobiolaging.2017.09.027

100. Ko H, Ihm J-J, Kim H-G. Cognitive profiling related to cerebral amyloid burden using machine learning approaches. Front Aging Neurosci. 2019;11:95. https://doi.org/10.3389/fnagi.2019.00095

101. Pothier K, Saint-Aubert L, Hooper C, Delrieu J, Payoux P, Barreto PS, et al. Cognitive changes of older adults with an equivocal amyloid load. J Neurol. 2019;266(4):835-43. https://doi.org/10.1007/s00415-019-09203-5

102. Rabin JS, Perea RD, Buckley RF, Johnson KA, Sperling RA, Hedden T. Synergism between fornix microstructure and beta amyloid accelerates memory decline in clinically normal older adults. Neurobiol Aging. 2019;81:38-46. https://doi.org/10.1016/j.neurobiolaging.2019.05.005

103. Rahayel S, Bocti C, Sévigny Dupont P, Joannette M, Lavallée MM, Nikelski J, et al. Subcortical amyloid relates to cortical morphology in cognitively normal individuals. Eur J Nucl Med Mol Imaging. 2019;46(4):835-49. https://doi.org/10.1007/s00259-019-04446-w

104. Yu L, Petyuk VA, Tasaki S, Boyle P, Gaiteri C, Schneider JA, et al. Association of cortical β-amyloid protein in the absence of insoluble deposits with alzheimer disease. JAMA Neurol. 2019;76(7):818-26. https://doi.org/10.1001/jamaneurol.2019.0834

105. Dupont PS, Bocti C, Joannette M, Lavallée MM, Nikelski J, Valet GT, et al. Amyloid burden and white matter hyperintensities mediate age-related cognitive differences. Neurobiol Aging. 2020;86:16-26. https://doi.org/10.1016/j.neurobiolaging.2019.08.025

106. Joannette M, Bocti C, Dupont PS, Lavallée MM, Nikelski J, Valet GT, et al. Education as a moderator of the relationship between episodic memory and amyloid load in normal aging. J Gerontol Ser A. 2020;75(10):1820-6. https://doi.org/10.1093/gerona/glz235

107. Lim YY, Maruff P, Kaneko N, Doeeke J, Fowler C, Villemagne VL, et al. Plasma Amyloid-β Biomarker Associated with Cognitive Decline in Preclinical Alzheimer’s Disease. J Alzheimers Dis. 2020;77(3):1057-65. https://doi.org/10.3233/JAD-200475

108. Squarzoni P, Faria D de P, Yasuda MS, Porto FHG, Coutinho AM, Costa NA, et al. Relationship between PET-assessed amyloid burden and visual and verbal episodic memory performance in elderly subjects. J Alzheimers Dis. 2020;78(1):229-44. https://doi.org/10.3233/JAD-200758

109. Busatto Filho G, Duran Fl, de S, Squarzoni P, Coutinho AM, Rosa PG, Torralbo L, et al. Hippocampal subregional volume changes in elders classified using positron emission tomography-based Alzheimer’s biomarkers of β-amyloid deposition and neurodegeneration. J Neurosci Res. 2021;99(2):481-501. https://doi.org/10.1002/jnr.24739

110. Han JW, Maillard P, Harvey D, Fletcher E, Martinez O, Johnson DK, et al. Association of vascular brain injury, neurodegeneration, amyloid, and cognitive trajectory. Neurology. 2020;95(19):e2622-34. https://doi.org/10.1212/WNL.0000000000010531