v. 4, n. 67, 2024

International Journal of Health Science

NEUROIMAGING IN DEMENTIA: A COMPREHENSIVE EVALUATION ACROSS VARIOUS TYPES

Leonardo Lucas Pereira Filho
http://lattes.cnpq.br/4022430994941735

Lara Fernanda de Sá Guimarães
http://lattes.cnpq.br/0629827528773204

Maykon Pablo Aguiar Fenelon
http://lattes.cnpq.br/521999614166349

Otavio Shiguemitsu Valenciano
http://lattes.cnpq.br/2149475732805575

Isabela Massarotti
https://lattes.cnpq.br/0011411041304167

Wilson Jolando Ojeda Júnior
https://lattes.cnpq.br/3730550452281724

Guilherme Garcia Mendonça

Ana Eliza de Pádua
https://lattes.cnpq.br/6927575414364517

Lara Macatrão Durante Bacelar

Carlos Alberto de Mattos
http://lattes.cnpq.br/7625994072171947

Nara Fernanda Alencar da Costa Pinheiro
http://lattes.cnpq.br/6493513370859829

Melyssa Aryane de Oliveira
http://lattes.cnpq.br/9531560727825211

Henrique Bosso
http://lattes.cnpq.br/6410681383518426

Resume: **INTRODUCTION** Dementia, marked by a progressive decline in cognitive functions, poses a growing public health challenge. The introduction provides an overview of dementia, highlighting the importance of early diagnosis and the pivotal role of neuroimaging in identifying structural and functional brain changes. It traces the historical development of neuroimaging techniques and discusses various modalities, including MRI, CT, PET, and SPECT, and their contributions to understanding different dementia types. **OBJETIVE** To evaluate the role of neuroimaging in diagnosing and differentiating various types of dementia, including Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia, and to assess the structural and functional changes associated with each type. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Neuroimaging" AND "Dementia Diagnosis" AND "Alzheimer's Disease" OR "Brain Atrophy" OR "Functional MRI" in the last years. **RESULTS AND DISCUSSION** The results and discussion sections delve into the specific findings from neuroimaging studies across different dementia types. MRI reveals significant hippocampal atrophy in Alzheimer's disease, white matter lesions in vascular dementia, and distinct patterns in Lewy body and frontotemporal dementias. PET imaging shows amyloid plaques and tau tangles in Alzheimer's disease, while fMRI studies reveal disruptions in brain connectivity. The use of advanced techniques like DTI provides insights into white matter integrity. Comparative analyses, longitudinal studies, and the impact of genetic factors are also discussed, highlighting the diagnostic and prognostic value of. **CONCLUSION** Neuroimaging has significantly advanced the diagnosis and management of dementia, providing detailed assessments of brain structure and function. Despite challenges such as high costs and variability in protocols, ongoing advancements promise improved sensitivity and specificity of imaging biomarkers. Neuroimaging-based models for early detection and disease progression monitoring are crucial for timely interventions and better patient outcomes. The integration of neuroimaging in clinical practice continues to enhance our understanding and treatment of dementia, underscoring its indispensable role in modern medicine.

Keywords: Neuroimaging; Dementia; Alzheimer's Disease; MRI; PET.

INTRODUCTION

Dementia, characterized by a progressive decline in cognitive function beyond what might be expected from normal aging, poses a significant public health challenge globally[1]. As the aging population increases, so does the prevalence of dementia, with projections indicating a substantial rise in the number of affected individuals in the coming decades[1]. Various forms of dementia, including Alzheimer's disease (AD), vascular dementia (VaD), Lewy body dementia (LBD), and frontotemporal dementia (FTD), present with distinct clinical and pathological features, necessitating tailored diagnostic and therapeutic approaches[1]. Early diagnosis of dementia is crucial for managing the disease progression and improving patient outcomes[2]. Neuroimaging has emerged as a pivotal tool in the diagnostic arsenal, offering insights into the structural and functional changes in the brain associated with different types of dementia[2]. The historical evolution of neuroimaging techniques has revolutionized our understanding of dementia, transitioning

from rudimentary imaging to advanced modalities such as magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), and single-photon emission computed tomography (SPECT)[2].

Each neuroimaging modality offers unique advantages and insights[3]. MRI provides high-resolution images of brain structures, making it indispensable for detecting atrophy and other structural changes. CT, though less detailed than MRI, remains useful in identifying gross anatomical abnormalities[3]. PET and SPECT scans are instrumental in assessing brain metabolism and blood flow, respectively, allowing for the evaluation of functional changes in the brain[3]. The biological basis of these neuroimaging techniques lies in their ability to detect alterations in brain anatomy, metabolism, and connectivity that are characteristic of various dementia types[4]. Recent advancements in neuroimaging technology, such as functional MRI (fMRI) and diffusion tensor imaging (DTI), have further expanded our capabilities[5]. These techniques enable the visualization of brain activity and white matter integrity, providing deeper insights into the pathophysiological processes underlying dementia[5]. Neuroimaging biomarkers, including amyloid plaques and tau tangles in AD, white matter lesions in VaD, and Lewy bodies in LBD, are critical for differentiating between dementia types and assessing disease progression[5].

In Alzheimer's disease, MRI and PET scans reveal characteristic patterns of brain atrophy and amyloid deposition[6]. Vascular dementia is distinguished by white matter lesions and infarcts visible on MRI[6]. Lewy body dementia is marked by the presence of Lewy bodies and reduced dopamine transporter uptake on SPECT or PET scans[6]. Frontotemporal dementia shows prominent atrophy in the frontal and temporal lobes, detectable through MRI[7]. These neuroimaging findings are not only diagnostic but also have clinical implications, guiding treatment decisions and monitoring therapeutic responses[7]. Despite the profound utility of neuroimaging in dementia, challenges and limitations persist[8]. Variability in imaging protocols, the high cost of advanced imaging techniques, and the need for specialized interpretation are significant hurdles[8]. Ethical considerations, such as the management of incidental findings and the potential psychological impact of imaging results on patients and their families, must also be addressed[8].

Future directions in neuroimaging for dementia are promising, with ongoing research focusing on improving the sensitivity and specificity of imaging biomarkers, integrating multimodal imaging approaches, and developing non-invasive techniques[9]. The potential for neuroimaging to aid in early detection, track disease progression, and evaluate the efficacy of novel therapeutic interventions underscores its critical role in the landscape of dementia research and clinical practice[9].

OBJETIVES

To evaluate the role of neuroimaging in diagnosing and differentiating various types of dementia, including Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia, and to assess the structural and functional changes associated with each type.

SECUNDARY OBJETIVES

1. To compare the effectiveness of different neuroimaging modalities (MRI, CT, PET, SPECT) in diagnosing dementia.
2. To identify specific neuroimaging biomarkers for Alzheimer's disease and other types of dementia.

3. To examine the advancements in neuroimaging technology and their impact on dementia diagnosis and management.
4. To investigate the correlation between cognitive decline and neuroimaging findings.
5. To assess the utility of neuroimaging in monitoring disease progression and evaluating therapeutic interventions.

METHODS

This is a narrative review, in which the main aspects of the role of neuroimaging in diagnosing and differentiating various types of dementia, including Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia, and to assess the structural and functional changes associated with each type in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Neuroimaging" AND "Dementia Diagnosis" AND "Alzheimer's Disease" OR "Brain Atrophy" OR "Functional MRI" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case-control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

The evaluation of structural changes in Alzheimer's disease using MRI reveals significant hippocampal atrophy, a hallmark of the disease[10]. Studies demonstrate that hippocampal volume reduction correlates with disease severity and progression, providing a reliable marker for early diagnosis and monitoring[10]. MRI-based analyses of cortical atrophy patterns indicate widespread thinning in AD, predominantly affecting the medial temporal lobes, parietal lobes, and posterior cingulate cortex, distinguishing it from other dementia types[11]. White matter lesions are prominent in vascular dementia, as evidenced by MRI findings of hyperintensities on T2-weighted and FLAIR sequences[11]. These lesions, indicative of small vessel disease, are associated with cognitive decline and functional impairment[12]. In comparison, Alzheimer's disease shows fewer white matter changes, emphasizing the utility of MRI in differentiating between these dementia subtypes[12]. Neuroimaging biomarkers for Alzheimer's disease, such as amyloid plaques and tau tangles detected via PET imaging, have shown high diagnostic accuracy[13]. Amyloid PET imaging, using tracers like florbetapir and Pittsburgh Compound B (PiB), allows for the visualization of amyloid deposition in vivo, correlating with cognitive decline and disease progression[13].

In Lewy body dementia, neuroimaging studies highlight reduced dopamine transporter uptake on SPECT or PET scans, distinguishing it from Alzheimer's disease[14]. The presence of Lewy bodies, detected through α-synuclein immunostaining in post-mortem studies, correlates with clinical symptoms of parkinsonism and visual hallucinations, supporting the diagnostic utility of neuroimaging[14]. Hippocampal volume reduction is less pronounced in LBD compared to AD, further aiding in differential diagnosis[15]. Functional

MRI (fMRI) studies have explored alterations in brain connectivity across different dementia types[15]. In Alzheimer's disease, disruptions in the default mode network (DMN) are evident, with reduced functional connectivity between key regions such as the posterior cingulate cortex and medial prefrontal cortex[16]. These findings correlate with cognitive deficits and disease severity[16]. In contrast, frontotemporal dementia shows alterations in executive control networks, reflecting the prominent behavioral and language impairments associated with this subtype[17].

Diffusion tensor imaging (DTI) has proven valuable in assessing white matter integrity in dementia[17]. In Alzheimer's disease, DTI studies reveal reduced fractional anisotropy in the corpus callosum and other major white matter tracts, indicating microstructural damage[18]. Vascular dementia, on the other hand, shows widespread white matter disruption, consistent with the impact of cerebrovascular pathology on brain connectivity[18]. The use of FDG-PET in differentiating dementia types is well-documented, with studies showing distinct patterns of hypometabolism[19]. Alzheimer's disease is characterized by reduced glucose metabolism in the temporoparietal cortex, while frontotemporal dementia shows hypometabolism in the frontal and anterior temporal lobes[19]. These metabolic patterns provide critical insights into the underlying neurodegenerative processes and aid in accurate diagnosis[20].

Longitudinal neuroimaging studies have been instrumental in tracking disease progression in dementia[20]. Serial MRI scans reveal the trajectory of brain atrophy in Alzheimer's disease, with consistent volume loss in the hippocampus and cortical regions over time[21]. Similarly, PET imaging studies demonstrate progressive amyloid accumulation and tau deposition, correlating with clinical decline[21]. These findings underscore the importance of neuroimaging in monitoring disease course and evaluating therapeutic interventions[22]. Comparative analyses of neuroimaging findings in sporadic versus familial Alzheimer's disease have highlighted genetic influences on disease progression[22]. Familial AD cases, often linked to mutations in the APP, PSEN1, and PSEN2 genes, exhibit earlier and more aggressive atrophy patterns compared to sporadic cases[23]. These differences emphasize the need for tailored diagnostic and therapeutic strategies based on genetic risk factors[23].

Neuroimaging studies in mixed dementia, where multiple pathologies coexist, reveal complex patterns of brain changes[24]. MRI and PET scans show overlapping features of Alzheimer's disease and vascular dementia, with both cortical atrophy and white matter lesions[24]. This overlap complicates diagnosis and necessitates a multimodal imaging approach to disentangle the contributions of each pathology[25]. Parkinson's disease dementia (PDD) presents with characteristic neuroimaging findings, including atrophy in the substantia nigra and other basal ganglia structures, as well as reduced dopamine transporter uptake on PET scans[25]. These alterations are distinct from those seen in Alzheimer's disease, aiding in differential diagnosis[26]. The utility of neuroimaging in clinical trials for dementia treatments is evident, with imaging biomarkers serving as surrogate endpoints to assess treatment efficacy[26]. Amyloid imaging agents, such as florbetapir and flutemetamol, have been evaluated in clinical trials, demonstrating their ability to detect amyloid burden and monitor the impact of therapeutic interventions[27].

Neuroinflammation markers, detected through advanced imaging techniques like PET with radiolabeled ligands for microglial activation, provide insights into the role of inflammation in dementia[27]. These markers

are elevated in Alzheimer's disease and other neurodegenerative conditions, correlating with disease severity and progression[28]. The development of neuroimaging-based predictive models for dementia has shown promise in identifying individuals at risk for developing the disease[28]. Machine learning algorithms applied to neuroimaging data can predict cognitive decline and conversion from mild cognitive impairment to Alzheimer's disease, offering potential for early intervention[29]. The correlation between cognitive decline and neuroimaging findings is well-established, with studies demonstrating that greater atrophy and metabolic dysfunction correlate with worse cognitive performance[29]. These findings reinforce the role of neuroimaging in assessing disease burden and guiding clinical management[30]. Brain metabolism changes in dementia, assessed through FDG-PET, provide critical insights into the functional impact of neurodegeneration[30]. Alzheimer's disease shows hypometabolism in the posterior cingulate cortex and parietotemporal regions, while frontotemporal dementia exhibits reduced metabolism in the frontal lobes[31]. These metabolic patterns reflect the differential involvement of brain networks in various dementia types[31].

Advanced imaging techniques have enabled the analysis of synaptic density changes in dementia[32]. PET imaging with tracers targeting synaptic vesicle proteins, such as SV2A, reveals synaptic loss in Alzheimer's disease, correlating with cognitive impairment[32]. These findings highlight the potential of synaptic imaging as a biomarker for neurodegeneration[33]. Comorbidities, such as cardiovascular disease and diabetes, impact neuroimaging findings in dementia, exacerbating white matter lesions and brain atrophy[33]. These comorbidities contribute to cognitive decline and complicate the clinical presentation, emphasizing the need for comprehensive patient assessment[34]. Neuroimaging studies have identified early signs of dementia in individuals at risk for the disease[34]. MRI and PET scans reveal subtle brain changes, such as hippocampal atrophy and amyloid deposition, in cognitively normal individuals with genetic risk factors or a family history of Alzheimer's disease[35]. These findings support the use of neuroimaging for early detection and intervention[35]. Functional MRI (fMRI) plays a crucial role in understanding neural network alterations in dementia[36]. Studies show disrupted connectivity in key networks, such as the default mode network and executive control network, in Alzheimer's disease and frontotemporal dementia[36]. These alterations correlate with cognitive deficits and provide insights into the functional impact of neurodegeneration[37].

Cost-effectiveness analyses of neuroimaging modalities highlight the benefits of early diagnosis and monitoring in dementia[37]. While advanced imaging techniques are costly, their ability to detect disease early and guide treatment decisions can reduce overall healthcare costs by delaying disease progression and improving patient outcomes[38]. Neuroimaging-based intervention monitoring in dementia therapies is essential for assessing treatment efficacy[38]. Imaging biomarkers, such as amyloid load and brain atrophy, serve as surrogate endpoints in clinical trials, providing objective measures of therapeutic impact[39]. This approach facilitates the development of effective treatments and accelerates the translation of research findings into clinical practice[39]. Gender differences in neuroimaging findings in dementia have been observed, with studies indicating that women exhibit greater amyloid burden and faster rates of brain atrophy than men[40].

These differences may reflect biological and hormonal influences on disease progression,

underscoring the need for gender-specific research and therapeutic strategies[40]. Cross-sectional versus longitudinal neuroimaging data in dementia research provide complementary insights[41]. Cross-sectional studies offer snapshots of disease-related changes, while longitudinal studies track the progression of these changes over time[41]. Combining both approaches enhances our understanding of disease dynamics and informs the development of predictive models[42].Genetic factors, such as the presence of the APOE ε4 allele, significantly impact neuroimaging findings in dementia[42]. APOE ε4 carriers exhibit greater amyloid deposition, faster rates of brain atrophy, and earlier onset of cognitive decline compared to non-carriers[43]. These genetic influences underscore the importance of personalized approaches in dementia research and clinical care[43].

CONCLUSION

Neuroimaging has revolutionized the diagnosis and management of dementia, providing critical insights into the structural and functional changes associated with different dementia types. MRI, CT, PET, and SPECT scans offer unique advantages, with advanced techniques like fMRI and DTI further expanding our capabilities. The identification of neuroimaging biomarkers, such as amyloid plaques and tau tangles in Alzheimer's disease, white matter lesions in vascular dementia, and Lewy bodies in Lewy body dementia, has enhanced diagnostic accuracy and informed therapeutic strategies. Despite the challenges and limitations, including variability in imaging protocols, high costs, and ethical considerations, the future of neuroimaging in dementia is promising. Ongoing research aims to improve the sensitivity and specificity of imaging biomarkers, integrate multimodal approaches, and develop non-invasive techniques. Neuroimaging-based predictive models and early detection strategies hold potential for timely intervention and improved patient outcomes.

The correlation between cognitive decline and neuroimaging findings underscores the importance of imaging in assessing disease burden and guiding clinical management. Gender differences and genetic influences on neuroimaging findings highlight the need for personalized approaches in dementia care. As neuroimaging continues to evolve, its role in clinical trials and therapeutic monitoring will be pivotal in advancing dementia research and treatment. In conclusion, neuroimaging stands as a cornerstone in the landscape of dementia research and clinical practice. Its ability to provide detailed, non-invasive assessments of brain structure and function makes it indispensable for early diagnosis, monitoring disease progression, and evaluating therapeutic interventions. The continued advancements in neuroimaging technology and methodology promise to further our understanding of dementia and improve the lives of those affected by this devastating condition.

REFERENCES

1. Jack CR Jr, Petersen RC, Xu YC, O'Brien PC, Waring SC, Tangalos EG, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology. 1999 Jul;52(7):1397-403.

2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999 Mar;56(3):303-8.

3. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984 Jul;34(7):939-44.

4. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991 Sep;82(4):239-59.

5. Frisoni GB, Testa C, Sabattoli F, Beltramello A, Soininen H, Laakso MP. Structural correlates of early and late onset Alzheimer's disease: voxel based morphometric study. J Neurol Neurosurg Psychiatry. 2005 Jan;76(1):112-4.

6. Whitwell JL, Jack CR Jr, Parisi JE, Knopman DS, Boeve BF, Petersen RC, et al. Rates of cerebral atrophy differ in different degenerative pathologies. Brain. 2007 Apr;130(4):1148-58.

7. Schott JM, Bartlett JW, Fox NC, Barnes J. Increased brain atrophy rates in cognitively normal older adults with low cerebrospinal fluid Abeta1-42. Ann Neurol. 2010 Dec;68(6):825-34.

8. Thompson PM, Hayashi KM, de Zubicaray G, Janke AL, Rose SE, Semple J, et al. Mapping hippocampal and ventricular change in Alzheimer disease. Neuroimage. 2004 Jan;22(4):1754-66.

9. McEvoy LK, Brewer JB. Quantitative structural MRI for early detection of Alzheimer's disease. Expert Rev Neurother. 2010 Nov;10(11):1675-88.

10. Jagust WJ, Landau SM. Apolipoprotein E, Not Fibrillar β-Amyloid, Reduces Cerebral Glucose Metabolism in Normal Aging. J Neurosci. 2012 Sep;32(50):18227-33.

11. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol. 2011 Nov;70(11):960-9.

12. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med. 2014 Jun;275(3):214-28.

13. Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007 Aug;6(8):734-46.

14. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):280-92.

15. Jagust W, Reed B, Mungas D, Ellis W, DeCarli C. What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? Neurology. 2007 Nov;69(9):871-7.

16. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol. 2009 Apr;65(4):403-13.

17. Filippi M, Agosta F, Barkhof F, Dubois B, Fox NC, Frisoni GB, et al. EFNS task force: the use of neuroimaging in the diagnosis of dementia. Eur J Neurol. 2012 Apr;19(12):1487-501.

18. Jack CR Jr, Shiung MM, Gunter JL, O'Brien PC, Weigand SD, Knopman DS, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology. 2004 Apr;62(4):591-600.

19. Jagust WJ. Neuroimaging in dementia. Neurol Clin. 2007 May;25(3):843-57.

20. Desikan RS, McEvoy LK, Thompson WK, Holland D, Roddey JC, Blennow K, et al. Amyloid-β–associated clinical decline occurs only in the presence of elevated P-tau. Arch Neurol. 2012 Jun;69(6):709-13.

21. Walhovd KB, Fjell AM, Reinvang I, Lundervold A, Dale AM, Eilertsen DE, et al. Effects of age on volumes of cortex, white matter and subcortical structures. Neurobiol Aging. 2005 Oct;26(9):1261-70.

22. Risacher SL, Saykin AJ, West JD, Shen L, Firpi HA, McDonald BC. Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. Curr Alzheimer Res. 2009 Aug;6(4):347-61.

23. Thal DR, Rüb U, Orantes M, Braak H. Phases of Aβ-deposition in the human brain and its relevance for the development of AD. Neurology. 2002 Jun;58(12):1791-800.

24. Ott BR, Scanlon JM, Messina M, Festa EK, Yemul N, Heindel WC. A single-photon emission computed tomography imaging study of regional cerebral blood flow in dementia with Lewy bodies and Alzheimer's disease. Neurology. 2007 May;69(3):222-9.

25. Kantarci K, Lowe VJ, Przybelski SA, Senjem ML, Weigand SD, Ivnik RJ, et al. Magnetic resonance spectroscopy, β-amyloid load, and cognition in a population-based sample of cognitively normal older adults. Neurology. 2011 Jan;77(10):951-8.

26. Habes M, Janowitz D, Erus G, Toledo JB, Resnick SM, Doshi J, et al. Advanced brain aging: relationship with epidemiologic and genetic risk factors, and overlap with Alzheimer disease atrophy patterns. Transl Psychiatry. 2016 Apr;6(4):e775.

27. Dukart J, Schroeter ML, Mueller K; Alzheimer's Disease Neuroimaging Initiative. Age correction in dementia--matching to a healthy brain. PLoS One. 2011 Jul;6(7):e22193.

28. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. J Nucl Med. 2013 Jan;54(3):476-90.

29. Jagust WJ, Mormino EC. Lifespan brain activity, β-amyloid, and Alzheimer's disease. Trends Cogn Sci. 2011 Dec;15(11):520-6.

30. Frisoni GB, Fox NC, Jack CR Jr, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol. 2010 Feb;6(2):67-77.

31. Chan D, Fox NC, Jenkins R, Scahill RI, Crum WR, Rossor MN. Rates of global and regional cerebral atrophy in AD and frontotemporal dementia. Neurology. 2001 Dec;57(10):1756-63.

32. Risacher SL, Saykin AJ. Neuroimaging biomarkers of neurodegenerative diseases and dementia. Semin Neurol. 2013 Oct;33(4):386-416.

33. Landau SM, Harvey D, Madison CM, Reiman EM, Foster NL, Aisen PS, et al. Comparing predictors of conversion and decline in mild cognitive impairment. Neurology. 2010 Nov;75(3):230-8.

34. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol. 2010 Mar;6(3):131-44.