Toward MRI-based whole-brain health assessment: The brain atrophy and lesion index (BALI)

Lukas A. Grajauskas¹,² | Hui Guo¹,³ | Ryan C.N. D’Arcy¹,² | Xiaowei Song¹,²

¹Health Sciences and Innovation, Fraser Health Authority, Surrey, BC, Canada
²ImageTech Laboratory, Simon Fraser University, Surrey, BC, Canada
³Diagnostic Imaging, Tianjin Medical University General Hospital, Tianjin, China

Correspondence
Xiaowei Song, ImageTech Laboratory, Surrey Memorial Hospital, Surrey, BC, Canada.
Email: xiaowei.song@fraserhealth.ca

Funding information
Canada’s National Science and Engineering Research Council, Grant/Award Number: Alexander Graham Bell graduate research fellowship; China Scholarship Council, Grant/Award Number: Fellowship Award; Canadian Institutes of Health Research, Grant/Award Number: CSE-125739; Surrey Hospital and Outpatient Centre Foundation, Grant/Award Number: FHREB2015-030

Abstract
There have been many attempts to assess the elements of age- and dementia-related neurodegenerative changes in the brain using MRI; however, traditionally assessments focus only on single deficit. Over the past few years, our group has worked to create and validate the Brain Atrophy and Lesion Index (BALI) as an MRI-based whole-brain structural degeneration rating scale. The BALI can be used for applications in aging and dementia across the entire brain and can be applied to common clinical MR images. As a whole-brain structural health assessment, the BALI gives a more representative picture of how the brain ages. During the aging process, multiple elements of degeneration accumulate and interact to overwhelm repair processes and cause high-level failure in the function of the brain. To reflect this process, the BALI combines the assessment of several neurodegeneration changes into one scale. The BALI evaluation can be performed quickly and has been validated for use by non-neuroradiology expert raters trained with the method. This review gives a brief overview of the content of the BALI; covers the development, refinement, and application of the method; and provides insights about future development and clinical implementation of MRI-based whole-brain health assessment in aging and dementia.

KEYWORDS
Alzheimer’s disease, brain aging, brain atrophy and lesion index, dementia, magnetic resonance imaging

1 | INTRODUCTION

As we age, structural degeneration occurs throughout the brain. These degenerative changes are nearly inescapable; they are seen in normal aging, and with increased severity in individuals with dementia and cognitive decline.¹-⁴ Some of these, such as atrophy and white matter lesions, are well recognized as markers of cognitive decline and dementia,⁵,⁶ and others, such as dilated perivascular spaces and microvascular changes, have received less attention.¹ While most literature has focused on evaluating the impact of each of these changes, a number of studies have noted that certain changes are more likely to occur in tandem and can combine to increase the risk of cognitive decline and dementia.⁷-¹⁰ This makes intuitive sense. As a complex and interconnected system, the activities of the brain can be disrupted not only by a large insult, but also by diffuse damage from multiple smaller deficits across subsystems. While the individual effect of each of these small changes may be minor, their combined impact can cumulate to produce negative outcomes in the higher-level functions of the brain. While research has pointed to this cumulative impact of small changes on general health,¹¹ a standardized methodology for assessing neurodegenerative changes across the entire brain is yet to be established.

Even though it has not been extensively utilized to address this specific problem, magnetic resonance imaging (MRI) is a superb...
modality for the assessment of structural changes in the brain. While these structural changes result from a number of underlying pathologies, they result in several characteristic changes that are visible on MR images taken using common clinical sequences. Clinicians and scientists have created a number of scales to be applied to MRI that quantify individual neurodegenerative changes, such as Scheltens’ Medial Temporal Atrophy Scale (MTAS)12 and the Fazekas Scale for White Matter Lesions.13 However, these scales are incapable of assessing multiple changes across the entire brain simultaneously. The MRI-based “Brain Atrophy and Lesion Index” (BALI) has been created and validated to address this deficiency. The BALI is a semi-quantitative visual scale that adapts and combines several established evaluation methods that typically target specific types of brain changes in specific brain regions, to give a measure of whole-brain structural degeneration, with applications in aging and dementia research and for future clinical translation. In this paper, we introduce the BALI method and give an overview of how it was validated and applied to different research questions.

2 | CONTENT OF THE BALI

To produce a BALI score, several subcategories are assessed, primarily using either T1- or T2-weighted images which are common in research and routine clinical MRI tests (while other clinical sequences can also be added to the assessment when available). A score of 0-3 is assigned based on the severity of the changes occurring in each category. Scores of 4 and 5 possible in the deep white matter and the global atrophy categories, which allows us to account for very severe changes. Subcategory scores are summed to a total score with a maximum of 25. The BALI can be rated on both 1.5T and 3T images,9 and images from other common clinical MRI sequences can be included to increase our ability to see specific changes.10 Table 1 describes the BALI evaluation method of how images are rated. Figure 1 gives examples of the BALI rating of two older adult individuals with the same age and sex. For a more comprehensive account of how the BALI can be implemented, see Guo et al.14

2.1 | Category 1: Gray matter lesions and subcortical dilated perivascular spaces (GM-SV)

This category assesses any lesions within the cortical gray matter, such as small areas of encephalomalacia, and juxtacortical dilated perivascular spaces.

2.2 | Category 2: Deep white matter lesions (DWM)

This category assesses white matter hyperintensities located in the white matter, excluding the periventricular and juxtacortical WM. Scores of 4 and 5 are given when there are extensive white matter lesions throughout the entire brain.

2.3 | Category 3: Periventricular white matter lesions (PV)

This category assesses lesions in the white matter adjacent to the lateral ventricles. White matter hyperintensities are the lesion type most often seen here.

2.4 | Category 4: Lesions in the basal ganglia and surrounding areas (BG)

This includes lesions in the caudate nucleus, putamen, globus pallidus, internal capsule, thalamus, external capsule, claustrum, and insular

---

**TABLE 1** Evaluation schema of the brain atrophy and lesion index (BALI)

| Categories       | Description                                                                 | Rating schema                                                                 |
|------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| GM-SV            | Gray matter lesions and subcortical dilated perivascular spaces              | 0 = absence; 1 = dotted abnormal SI in GM or multiple dotted/liner abnormal SI in subcortical areas; 2 = small patches of abnormal SI in GM or diffuse and countless dotted/liner abnormal SI in subcortical areas; 3 = patches of abnormal SI in GM |
| DWM              | Deep white matter lesions                                                    | 0 = absence; 1 = dotted abnormal SI; 2 = small patches of abnormal SI; 3 = large patchy abnormal SI lesions; 4 = large patchy abnormal SI involving all cerebral lobes; 5 = abnormal SI involving complete deep WM |
| PV               | Periventricular white matter lesions                                        | 0 = absence; 1 = “cap” or pencil-thin lining; 2 = smooth “halo” with blurred margin; 3 = irregular periventricular abnormal signal intensities extending into the deep WM |
| BG               | Lesions in the basal ganglia and surrounding areas                           | 0 = absence; 1 = 1 focal lesion; 2 = more than 1 focal lesion; 3 = patchy confluent lesions (regardless of dilated perivascular spaces) |
| IT               | Lesions in the infratentorial regions                                        | 0 = absence; 1 = 1 focal lesion; 2 = more than 1 focal lesion; 3 = patchy confluent lesions |
| GA               | Global atrophy                                                              | 0 = no obvious atrophy; 1 = mild atrophy; 2 = moderate atrophy; 3 = severe atrophy; 4 = most severe atrophy present especially in the medial temporal lobes; 5 = most severe atrophy present especially in the medial temporal lobes and cerebral cortex |
| MH               | Microhemorrhage                                                             | 0 = absence; 1 = 1 focal lesion; 2 = more than 1 focal lesion; 3 = diffuse lesions |
| Other findings   | Neoplasm, trauma, deformity, hydrocephalus                                  | 0 = no other kind of finding; 1 = any one kind; 2 = any two kinds; 3 = more than two kinds |

GM, gray matter; SI, signal intensity; WM, white matter.
**FIGURE 1** Examples showing the evaluation of the Brain Atrophy and Lesion Index (BALI) using T1-weighted MRI. Case 1: 83 y, F, AD; Case 2: 84 y, F, HC. BG, lesions in the basal ganglia and surrounding areas; DWM, deep white matter lesions; GA, global atrophy; GM-SV, gray matter lesions and subcortical dilated perivascular spaces; IT, lesions in the infratentorial compartment; PV, periventricular white matter lesions.
lobes. Lesions here are primarily lacunar infarcts. Dilated perivascular spaces seen in the ventral aspects of the BG along the path of the lenticulostriate arteries are not rated, as these are seen in high prevalence even in younger individuals, and may not represent the result of a pathological process.
2.5 | Category 5: Lesions in the infratentorial compartment (IT)

This category includes lesions in the brainstem (medulla oblongata, pons, and midbrain) and cerebellum. The lesions most often result from small vessel ischemic changes and lacunar infarcts.

2.6 | Category 6: Global atrophy

This assesses atrophy across the entire brain, including enlargement of ventricles and sulci. Scores of 4 and 5 are given when severe atrophy is seen in the medial temporal lobes.

2.7 | Category 7: Other findings

This can include any other abnormal finding seen in the aging brain not categorized previously. These can include hydrocephalus, malformations, and neoplasm. When applying the BALI to large multicenter research datasets, findings in this category are rare, as these findings are often exclusion criteria for the studies.

3 | DEVELOPMENT OF THE BALI

Since its inception, the BALI has undergone several refinements and contributed to the research field in various ways. The first work to introduce the BALI applied the index to a sample of images collected.
by our group (n = 140), as well as images collected in the first phase of Alzheimer’s Disease Neuroimaging Initiative (ADNI) study (n = 153), a large multicenter initiative that gives researchers access to neuroimaging data, as well as other measures. T1WI and T2WI were rated separately by two radiologists using BALI (Table 1). The results showed a high correlation between ratings performed on images using each sequence and were highly correlated with age and cognitive performance. The BALI scores were also sensitive in their ability to detect group differences, helping delineate Alzheimer’s disease (AD), mild cognitive impairment (MCI), and healthy controls (HC). Furthermore, this initial work also supported the hypothesis that the summed effect of the lesions is more important than each considered in isolation, as the total BALI score was better correlated with age and cognition than the individual lesion scores, even those considered to be traditional hallmarks of age-related neurodegeneration.

After its introduction, a follow-up study by Zhang et al investigated whether the tool could be used to evaluate the progression of brain structural changes over time. To achieve this, ADNI MR images from the baseline assessment, and from the 24-month follow-up, were rated. Mean BALI scores at baseline and follow-up were significantly related to both Mini-Mental State Examination (MMSE) and Alzheimer’s Disease Assessment Scale-Cog (ADAS-Cog) scores. The change in BALI from baseline to follow-up was also associated with the change in MMSE (though not ADAS-Cog), and further, the participants who showed stable or improved MMSE also had stable or improved BALI. During the follow-up period, a number of MCI participants converted to AD. The AD and MCI-AD converters showed the highest BALI values, while the difference between BALI scores for the HC group and the nonconverting MCI participants was not statistically significant. While no participants regressed from AD-MCI, there were a few participants that showed an improvement in their BALI score, a promising sign. However, no treatment data are included in the ADNI dataset, so it is unclear as to the exact cause of this improvement.

Building upon this, Song et al investigated the dynamics of brain aging and neurodegeneration. Here, the BALI was applied to investigate the hypothesis of cognitive dynamics, which suggests that the state of the aging brain is the product of interactions between the processes that impair cognitive function and opposing repair processes that work to resist and counteract this degeneration. While most cases of improvement in cognitive function are the product of therapeutic interventions, there have been reports, even from the pretreatment era, of improvement in cognitive function and structural brain improvement. This theory builds upon a prominent study performed at the Mayo Clinic that showed that a portion of MCI participants could show cognitive improvement. In the investigation of cognitive dynamics, several associated papers have investigated dynamics in cognitive scores, but a much more interesting analysis would be a measure of neuroanatomy.

Song et al did this, using a multistate transition model. Cognitive measures (ADAS-Cog and MMSE), as well as the neuroanatomical measures of the MTAS and BALI score, were divided into discreet states, with the transition between the states being investigated. The average trend in all measures was worsening, but despite this, a portion of participants were shown to have improved in each of these scores. An improvement in BALI score was associated with a better chance of improvement in cognitive test scores. Of note, none of the participants that showed improvement in the BALI were diagnosed with AD in the follow-up period. Only one person showed a decrease in the MTAS score, but this participant also showed improvement in BALI, MMSE, and ADAS-Cog scores. The subsections that showed the most improvement recorded by the BALI were periventricular lesions, DWM, and infratentorial structures, suggesting that more change might be possible in areas that are related to vascular injury/damage. While instrumental factors cannot be entirely discounted, there was predictive validity in the fact that no one with an improvement in their BALI score over the follow-up was diagnosed with AD, and the concurrent validity of the associated scores lent credence to this analysis.

Literature has reported that variety of interventions can lead to structural brain improvements even in older adults with dementia. The improvements seen in BALI may have been the result of neuroplasticity, WM repair, improvements in cerebral circulation, brought on by an intervention, changes in nutrition or metabolism, or some other factors. This opens interesting possibilities to the ideas about neuroprotection and the dynamic nature of brain aging, and interesting possibilities for how the BALI can be implemented to track and research improvements in brain structure.

In another application of the BALI, Zhang et al investigated the association between BALI and MTAS scores in the prediction of dementia. The findings showed the scores correlated with one another, and within each, scores were significantly different across diagnostic groups. The 2-year MCI-AD conversion was significantly associated with both BALI and MTAS. A high BALI score was associated with an increased risk of MCI-AD conversion, and if combined with a high MTAS score, the risk was even greater; this combined score offered a high predictive accuracy. This is in line with the theory behind the BALI, which posits that combining multiple measures of neurodegeneration can give us a better picture of the aging brain. While the BALI gives a highly generalizable measure of brain aging, the MTAS gives us a very specific measure of focal atrophy symbolizing Alzheimer’s disease process. This opens up the possibility that re-weighting the BALI scores to emphasize MTA may be beneficial for the prediction of AD; however, doing so would reduce the generalizability of the BALI. Further work may create differently weighted versions of the BALI for use in different situations. In contrast though, recent work emphasizes the multiple structural deficits that present in AD, particularly vascular risk factors, which may be some of the first changes to present in the neurodegenerative process: even though the BALI may not be specific to underlying pathology of a deficit, it is open to many more aspects of the disease process.

To extend the capabilities of the BALI, further work was carried out to validate its use on both 3.0T and conventional 1.5T images. Guo et al made use of one of the unique aspects of the ADNI
et al.14 showed that researchers with a working knowledge of neuroanatomy and MRI can be taught how to use the scale, and they can produce data with inter- and intrarater reliability similar to that achieved by neuroradiologists. This increases the feasibility of BALI being mastered for use in different clinical and research settings.

Further work validated the application of the BALI to two more types of common clinical MRI sequences and assessed which types of images could best detect specific age-related changes. Guo et al.10 used 3T MR images from ADNI 2 (n = 950), the National Alzheimer’s Coordinating Center Uniform Data Set (n = 722), as well as a local dataset generated from multiple research protocols at a MRI center (n = 170). Scores showed a characteristic pattern across all datasets, supporting the assertion that the BALI scale can be easily applied to data collected under different protocols, and to a diverse range of participants. In this study, alongside the previously validated sequences (T1 and T2), clinical T2*GRE and T2 FLAIR images were included, while the images were examined to determine which type would most effectively reveal specific changes.10 The investigation revealed that T2WI are best for GM and subcortical lesions; T2FLAIR images were best for DWM and PV, and suitable for investigating the BG and GA; T1WI and T2WI are also suitable for BG and GA, and well suited for investigating malacia and others category. While T2*GRE is not suitable for rating the traditional BALI categories due to patchy low signal intensity, it is optimal for detecting microbleeds and lacunes with hemosiderin deposition. This work also initiated the BALI evaluation of microhemorrhages, which are of an increasingly high interest in aging research, as they are highly prevalent in aging populations. They have been implicated as an early presenting and high-impact change, in line with increasing evidence of the vascular contribution in Alzheimer’s disease process, and suggesting that vascular changes may be the first structural brain deficits contributing to AD. To further confirm the applicability of the four MRI sequences, Shi et al.26 applied similar methodology to a Chinese sample consisting of middle-aged and older adults and came to the same conclusions.

Although the integration of several MRI sequences makes the rating more time-consuming and complex, it creates another use case where more information and specificity can be obtained when multiple sequences are available. Further, one of the future possibilities of the BALI is automated or computer-aided solutions, and in this case, the use of multiple sequences will present less of a problem.

Several other studies are currently underway. These apply the BALI in new ways and take advantage of multiple independent datasets to improve generalizability, as well as new sources of information, such as longitudinal data, biomarkers, and lifestyle and protective factors evaluations to better understand the origin and determinants of brain health changes in aging. The BALI is an effective research tool that will allow for the continued investigation of novel research questions, and with further work, the BALI also stands to become a useful clinical tool, with important applications for our aging population.

4 | BALI VALIDATIONS

The development of new scales in MRI is always made complicated by the difficulty in obtaining a “ground truth.” When using a technique designed to be noninvasive and in vivo, there is little opportunity for neuroanatomical or histopathological investigation—which could be considered the gold standard—as this would require postmortem investigation. While this is challenging, one advantage of the BALI is the fact that is based on already well-established scales, and is grounded in physiological constructs that have had such postmortem investigations; for instance, correlations have been shown between in vivo and postmortem MRI with histopathological investigation of dilated perivascular spaces,27 which additionally confirmed the possibility of distinguishing dilated perivascular spaces from lacunes using MRI, giving support to MRI-based rating scales including dilated perivascular spaces.28

In addition to the fact that the BALI is based on a number of well-validated scales, there are a number of factors that further support the validity of the BALI. The whole-brain assessment has shown strong criterion validity, as BALI scores have a robust correlation with other measures that are associated with brain aging, such as MMSE, ADAS-Cog scores, Montreal Cognitive Assessment (MoCA), age, AD diagnosis, MTAS, and these patterns appear across multiple datasets, and in a diverse set of participants.9,10,14,15,17,18,24

Construct validity is also strong for the BALI. This concept refers to how well a scale can quantify aspects of the theoretical construct that are purported to measure. This then reflects both
the target measures, that is, the theoretical construct we are trying to quantify, and how well the two of them align. The theoretical construct the BALI aims to measure is “age-related whole-brain changes.” While one weakness of MRI is that it measures the outcome of age-related neurodegeneration rather than the pathophysiological processes that underlie it, MRI visible changes do occur in close synchrony with cellular- and vascular-level changes, especially with the added specificity offered by high-field images. Compared to other MRI measures that already exist, the BALI is much better suited to measure “brain aging,” as it takes a holistic approach, assessing changes across the entire brain. This is a more complete way to operationalize “brain aging,” as it is a heterogeneous process that occurs over the entire brain, and in many unique patterns across different individuals. Therefore, while the measure of a single brain change may be more specific, a holistic measure like the BALI will be more generalizable across the entire population. Alongside this, MRI allows for the measure to be applied in vivo, something not possible with histopathological measures capable of directly assessing pathophysiology.

The BALI was also shown to possess predictive validity, with work showing that a high BALI score is associated with a risk of MCI-AD conversion and that the combination of the BALI with other measures, such as the MTAS, may offer even greater predictive power.17,18,24

Overall, the BALI is shown to have strong internal validity, with strong inter-rater reliability and robust inter-rater reliability, shown repeatedly even with non-neuroradiologist raters. The BALI has also been shown to perform similarly on multiple datasets, collected in multiple countries under a number of different protocols.

5 | FUTURE OF WHOLE-BRAIN HEALTH ASSESSMENTS

A few other recent studies have also accounted for more than one type of brain changes using MRI, but they have not taken a whole-brain approach, while emerging whole-brain approaches lack the breadth of accounting for multiple changes.29,30 As the first validated MRI assessment of whole-brain health in aging, a number of future refinements and applications exist for the BALI.

In the process of its development, BALI has been applied to rating MR images from over three thousand participants, many of which were collected in large multicenter collaborations, giving access to a number of other tests, including cognitive assessments and various biomarkers. Further included datasets have extensive longitudinal data on the participants we assessed. Alongside further investigations utilizing cognitive and biomarker data, this set of rated images is a valuable resource for technical development. These data will allow further studies using machine-learning tools to train an automated classifier capable of producing a BALI score without relying on the expertise of a trained rater. Such an automated BALI assessment tool will have implications in both the research and clinical domains, allowing us to investigate trends by applying the BALI to even larger datasets, and giving clinicians a tool they can use to easily to track and assess the structural degeneration in the brains of their patients. Automated assessments will also allow us to do an in-depth investigation on the weighting of BALI subcategories, possibly increasing diagnostic specificity for various types of dementia. The potential applications of the BALI are numerous, and are well poised to make significant impacts on a number of problems currently faced by our society.

6 | CONCLUSION

Aging populations across the world are poised to cause significant social and economic problems. Dementia is estimated to effect 46.8 million people globally, at an annual cost of $818 billion USD,31 and even subclinical cognitive decline has an economic impact, and negatively affects the lives of those suffering and their families. Valid new tools that give us the capability to investigate how the brain ages will allow us to understand and tackle these problems much more effectively. The BALI is one such tool. In the case of Alzheimer’s, for over a decade, basic scientists and clinicians have looked for single protein abnormalities and failed to find a cohesive model of the disorder. It seems clear that rather than a single root cause, the disorder must more or less stem from a complex set of interacting deficits.32 The human brain is a complex system, with multiple redundancies and the capacity for active self-repair. Degeneration resulting from many deficits that combine to overwhelm these fail-safe systems makes more sense than failure resulting from a single insult. The BALI is designed to reflect this paradigm. Rather than investigating elements of neurodegeneration independently, it takes a holistic understanding, incorporating multiple elements, to reflect how failure must occur in a system as complex as the human brain. While there is still no clear way to reverse the course of cognitive decline and dementia, a great deal of evidence has shown that early intervention and modification of risk factors can delay the onset of the disorder. The BALI will help us do exactly that, both in its ability to help us learn about the aging brain and in its potential clinical applications.

ACKNOWLEDGMENTS

We would like to gratefully acknowledge Canada’s National Science and Engineering Research Council for providing funding to L. Grajauskas in the form of an Alexander Graham Bell graduate research fellowship; H. Guo received a Fellowship Award from China Scholarships Council to conduct research in Canada; operating grants from Canadian Institutes of Health Research (#CSE-125739) and Surrey Hospital and Outpatient Centre Foundation (#FHREB2015-030) to X. Song.

CONFLICT OF INTEREST

The authors declare that no conflicts of interest exist with this work.
REFERENCES

1. Boyle PA, Wilson RS, Yu L, et al. Much of late life cognitive decline is not due to common neurodegenerative pathologies. Ann Neurol. 2013;74:478-489.

2. van der Vlies AE, Staekenborg SS, Admiraal-Behloul F, et al. Associations between magnetic resonance imaging measures and neuropsychological impairment in early and late onset Alzheimer’s disease. J Alzheimer’s Dis. 2013;35:169-178.

3. Kim KW, MacFall JR, Payne ME. Classification of white matter lesions on magnetic resonance imaging in elderly persons. Biol Psychiatry. 2008;64:273-280.

4. Vernooy MW, Smits M. Structural neuroimaging in aging and Alzheimer’s disease. Neuroimaging Clin. 2012;22:33-55.

5. Drayer BP. Imaging of the aging brain. Part I. Normal findings. Radiology. 1988;166:785-796.

6. Black S, Gao F, Bilbao J. Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. Stroke. 2009;40(3 suppl 1):S48-S52.

7. Potter GM, Doubl FN, Jackson CA, et al. Enlarged perivascular spaces and cerebral small vessel disease. Int J Stroke. 2015;10:376-381.

8. Ding J, Sigurðsson S, Jónsson PV, et al. Large perivascular spaces visible on magnetic resonance imaging, cerebral small vessel disease progression, and risk of dementia. JAMA Neurol. 2017;74:1105.

9. Guo H, Song X, Vandorpe R, et al. Evaluation of common structural brain changes in aging and Alzheimer’s disease with the use of an MRI-based brain atrophy and lesion index: a comparison between T1WI and T2WI at 1.5T and 3T. Am J Neuroradiol. 2014;35:504-512.

10. Guo H, Siu W, D’Arcy RC, et al. MRI assessment of whole-brain structural changes in aging. Clin Interv Aging. 2017;12:1251-1270.

11. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007;62:722-727.

12. Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool WA. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. J Neurol. 1995;242:557-560.

13. Fazekas F, Barkhof F, Wahlund LO, et al. CT and MRI rating of white matter lesions. Cerebrovasc Dis. 2002;13(Suppl 2):31-36.

14. Guo H, Song X, Schmidt MH, et al. Evaluation of whole brain health in aging and Alzheimer’s disease: a standard procedure for scoring an MRI-based brain atrophy and lesion index. J Alzheimer’s Dis. 2014;42:691-703.

15. Chen W, Song X, Zhang Y, et al. An MRI-based semiquantitative index for the evaluation of brain atrophy and lesions in Alzheimer’s disease, mild cognitive impairment and normal aging. Dement Geriatr Cogn Disord. 2010;30:121-130.

16. Jack CR Jr, Bernstein MA, Fox NC, et al. The Alzheimer’s Disease Neuroimaging Initiative (ADNI): MRI methods. J Magn Reson Imaging. 2008;27:685-691.

17. Zhang N, Song X, Zhang Y, et al. An MRI brain atrophy and lesion index to assess the progression of structural changes in Alzheimer’s Disease, mild cognitive impairment, and normal aging: a follow-up study. J Alzheimer’s Dis. 2011;26:359-367.

18. Song X, Mitnitski A, Zhang N, Chen W, Rockwood K. Dynamics of brain structure and cognitive function in the Alzheimer’s disease neuroimaging initiative. J Neurol Neurosurg Psychiatry. 2013;84:17-78.

19. Roberts RO, Geda YE, Knopman DS, et al. The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic Study of Aging. Neurology. 2012;78:342-351. WNL-06013e3182452862.

20. Ganguli M, Snitz BE, Saxton JA, et al. Outcomes of mild cognitive impairment by definition: a population study. Arch Neurol. 2011;68:761-767.

21. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci. 2011;108:3017-3022.

22. Fotuhi M, Do D, Jack C. Modifiable factors that alter the size of the hippocampus with aging. Nat Rev Neurosci. 2012;8:189.

23. Belleville S, Clement F, Melah S, Gilbert B, Fontaine F, Gauthier S. Training-related brain plasticity in subjects at risk of developing Alzheimer’s disease. Brain. 2011;134:1623-1634.

24. Zhang N, Song X, Zhang Y. Combining structural brain changes improves the prediction of Alzheimer disease and mild cognitive impairment. Dement Geriatr Cogn Disord. 2012;33:318-326.

25. De Reuck J, Auger F, Durieux N, et al. Topography of cortical microbleeds in Alzheimer’s disease with and without cerebral amyloid angiopathy: a Post-Mortem 7.0-Tesla MRI Study. Aging Dis. 2015;6:437-443.

26. Shi Y, Sun Z, Guo H, Yin X, Song X, Zhang Y. MRI-based brain atrophy and lesion index assessment of whole brain-structural changes during aging. Chinese J Geriatr. 2018;37:27-31.

27. Bokura H, Kobayashi S, Yamaguchi S. Distinguishing silent lacunar infarction from enlarged Virchow-Robin spaces: a magnetic resonance imaging and pathological study. J Neurol. 1998;245:116-122.

28. Chen W, Song X, Zhang Y. Alzheimer’s Disease Neuroimaging Initiative. Assessment of the Virchow-Robin Spaces in Alzheimer disease, mild cognitive impairment, and normal aging, using high-field MR imaging. AJNR Am J Neuroradiol. 2011;32:1490-1495.

29. Jang JW, Park SY, Park YH, et al. A comprehensive visual rating scale of brain magnetic resonance imaging: application in elderly subjects with Alzheimer’s disease, mild cognitive impairment, and normal cognition. J Alzheimers Dis. 2015;44:1023-1034.

30. Boutet C, Rouffiane-Leclair L, Schneider F, et al. Visual assessment of age-related white matter hyperintensities using FLAIR images at 3 T: inter- and intra-rater agreement. Neurodegener Dis. 2016;16:279-283.

31. Wimo A, Guerchet M, Ali GC, et al. The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimer’s Dement. 2017;13:1-7.

32. Song X, Mitnitski A, Rockwood K. Age-related deficit accumulation and the risk of late-life dementia. Alzheimers Res Ther. 2014:6:54.