Heliyon 10 (2024) e37836

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

A computer approach to assess age-related changes of the brain white matter in Alzheimer's disease

Vania Karami [a], Giovanna Ricci [b], Giuliano Pesel [c], Giulio Nittari [a,*]

[a] School of Pharmaceutical Sciences and Health Products, University of Camerino, Camerino, (MC), Italy
[b] Department of Legal Medicine, University of Camerino, Camerino, (MC), Italy
[c] Health Directorate, Occupational Medicine Section, Trieste, (TS), Italy

ARTICLE INFO

Keywords:
Age-related brain variation
White matter
Alzheimer's disease
MRI
Aging

ABSTRACT

Background: Age is one of the major risk factors for Alzheimer's disease (AD) which is considered the most common adult-onset dementia. There is little information about age-related changes during brain dementia.
Methods: This study observed age-related variations in the brain throughout adulthood in magnetic resonance imaging (MRI) of the AD and healthy brains. The Open Access Series of Imaging Studies (OASIS) is used as a database. The method consists of design and develop a computer approach based on artificial intelligence (AI) to segment white matter (WM) from the MRI. Then, the number of pixels within the segmented white matter (WM) of the brain was calculated. Correlation was used to investigate age relation with WM changes in the normal and AD brain.
Results: The WM change with aging was more correlated in AD group (rAD = −0.505, p-value = 0.0007) than control group (rControl = −0.357, p-value = 0.0001).
Conclusion: Higher correlation of WM pixel counts with age in AD group approved that AD is characterized by the relevant involvement of the WM and age. Our approach gained additional information on the quantitative pathological changes associated with the AD as the most common brain disorder of the elderly.

1. Introduction

1.1. Alzheimer's disease and aging

Neurodegenerative disorders leading to dementia is a challenging disease for those affected [1]. Alzheimer's disease (AD) is the most form of dementia [2]. With aging, the risk of dementia particularly AD rises dramatically [3]. Investigation of the age-related changes of the brain during AD might provide a new insight to understand more about the disease, and its symptoms [4]. There is little information regarding age-related changes throughout AD, however, age-related variations on the normal human brain have been studied in different articles [5–12].

Abbreviations: **AD**, Alzheimer's disease; **WM**, White Matter; **GM**, Gray Matter; **MRI**, Magnetic Resonance Imaging; **OAS SIS**, Open Access Series of Imaging Studies; **T1-w**, T1-weighted; **CDR**, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.

* Corresponding author. School of Pharmaceutical Sciences and Health Products, University of Camerino, 62032, Camerino, Italy.
E-mail address: giulio.nittari@unicam.it (G. Nittari).

https://doi.org/10.1016/j.heliyon.2024.e37836
Received 1 July 2024; Received in revised form 23 August 2024; Accepted 11 September 2024
Available online 14 September 2024

1.2. Alzheimer's disease and white matter deterioration

In the evaluation of age-related brain changes, it is better to consider both white matter (WM), and gray matter (GM) parts of the brain. For a long time, AD has been considered as the GM disease and most studies assessed only GM volume decline with aging [9,10]. However, recently it has revealed that WM also involved and WM deterioration as a sign of neurodegeneration might increase dementia risk [13]. Based on the pathological evidence, WM damage even might occur independently of GM atrophy [13]. The results of previous researches about WM are different but essentially, they showed WM volume is steady or increases slight throughout adulthood (40- 50-year range) [14–16], and followed by a high decline (around 60 years old) [14–17]. In another study, GM volume loss in normal brain appeared to be a constant and linear function of age throughout adult life, whereas WM volume loss seems to be delayed until middle adult life [17].

1.3. Magnetic resonance imaging

Recent significant breakthroughs in magnetic resonance imaging (MRI) and computer technology have resulted in precise, reproducible, and quantitative assessments of brain morphometry [18–22]. We therefore conducted this study using MRI of healthy and AD individuals to quantitatively measure the age-related changes in WM.

2. Materials and methods

2.1. Subjects

The dataset in this study is Open Access Series of Imaging Studies (OASIS) database [23]. This database consists of a cross-sectional collection of MR images of 416 subjects, both men, and women (mostly women), aged between 33 and 96 years old (Table 1). The female subjects are more than the male because women live longer than men do on average and older age is one of the most criteria for AD [24].

In this study, all images are 3D T1-weighted (T1-w) MRI scans in X-Y planes. Subjects are differentiated to several groups based on a global clinical dementia rating (CDR) scale including normal with no dementia and CDR of 0, and with AD dementia including very mild AD (CDR = 0.5) and mild AD (CDR = 1). 181 subjects were without CDR and therefore they were not included. Table 1 shows the ranges of age, education levels, and gender of AD and healthy group.

2.2. Methods

Fig. 1 shows the procedure of this study. The first step is using brain MRI of AD patients and the final outputs are the effect of age on the WM in healthy and AD individuals.

The MRI scans were visually controlled (VK) to confirm that structural defects or technical artifacts were not present. Analysis of MRI data was done by the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (www.fmrib.ox.ac.uk/fsl) as our previous study [21].

Artificial intelligence model: we firstly designed and developed a new automatic artificial intelligence (AI) model to extract WM from the images. It uses Single-level discrete 2-D wavelet transform (2DWT) to extract features from the brain images [25]. Statistical features were defined in the distribution of the WM in the pixels of an image. In order to find the statistically significant features, features' comparison between groups (AD versus control) was done using statistical tests (P-values$<$0.05). The statistically selected features were first order statistical features including Contrast, Energy, Entropy, Mean, Root Mean Square (RMS), Standard Deviation, Skewness, Kurtosis, Variance, and Homogeneity (Table 2). These extracted features were used to identify the characteristic of the segmented WM and therefore, as input for the AI classification between early AD and healthy individuals. We chose 2DWT because it provides an efficient multi-resolution decomposition of images [26]. Principle component analysis (PCA) was used to reduce the dimensions of features [27].

Kernel support vector machine (KSVM) was used as classifier [28]. Data comparisons were adjusted for CDR, based on it, subjects are divided into two different classes, the first class includes patients with the AD (AD group) and the other class contains non-demented healthy subjects (control group).

To evaluate the performance of the AI to segment WM, the output of the WM segmentation was compared with the results of WM extracted from FSL as the gold standard. The comparison procedure was done by calculation of Sorensen-Dice similarity [29] between

Table 1
Summary of subject demographics and dementia status.

Group	AD	Normal
Age	62–92	33–94
CDR	0.5–1	0
MMSE	15–30	25–30
Education	1–5	1–5

Clinical Dementia Rating: CDR, Mini-Mental State Examination: MMSE.

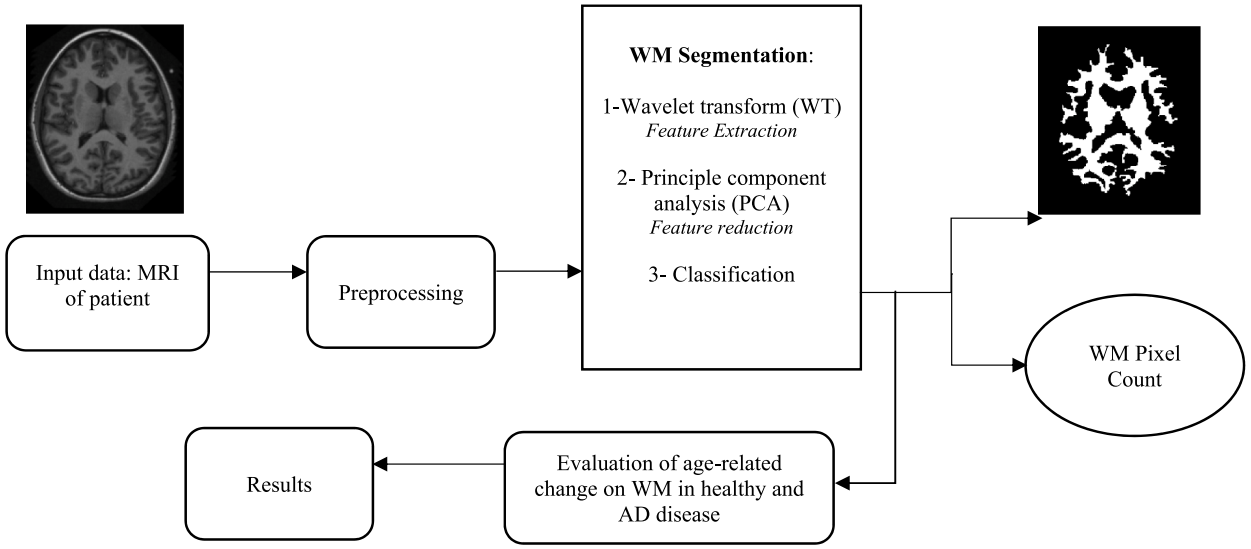


Fig. 1. Block diagram of the proposed method for the assessment of age-related WM changes throughout adulthood using magnetic resonance imaging (MRI).

Table 2
The extracted statistical features of the dataset.

CDR	CDR 0		CDR 0.5		CDR 1	
Mean, SD	Mean	SD	Mean	SD	Mean	SD
Contrast	0,28557	0,021301	0,28151	0,012408	0,28619	0,015661
Energy	0,77079	0,006166	0,77457	0,008604	0,76927	0,007893
Homogeneity	0,93524	0,001524	0,93644	0,002249	0,9348	0,002266
Mean	0,00383	0,001102	0,00346	0,000686	0,00397	0,000587
SD	0,08973	6,75E-05	0,08972	4,83E-05	0,08973	4,22E-05
Entropy	2,80456	0,063483	2,78092	0,034237	2,78764	0,038769
RMS	0,0898	0	0,17062	0	0,0898	0,255575
Variance	0,00809	4,22E-05	0,00809	3,16E-05	0,00808	3,16E-05
Kurtosis	12,49786	1,163231	12,78919	1,938669	12,93199	1,558777
Skewness	1,08466	0,16185	1,1595	0,142252	1,10997	0,214674

CDR: Clinical Dementia Rating, SD: Standard Deviation, RMS: Root Mean Square.

two binary images of the results and gold standard.

Pixel count: MRI is composed of the array of pixels in different brain areas. Pixel count is the number of pixels within a specified intensity range and has been recognized as a first-order statistical feature in the MRI studies [30]. The final output of the proposed computer aided system was the number of pixels for extracted WM of each subject.

Correlation analysis: Pixel count determination provided the possibility to quantitatively verify the age-related changes of WM for each subject. Spearman's correlation analysis [31] between age and pixel count as the volumetric variable was done in both groups of AD and control. Significant results were considered at $p < 0.05$.

All preprocessing and postprocessing of the MR images, as well as statistical analysis were performed using MATLAB R2022a.

3. Results

The results of WM segmentation using the proposed method showed an accurate performance (average Dice score = 0.891, $p < 0.001$, Fig. 2).

Fig. 3 shows the trends of changing WM during aging in control and AD groups. The black point sets represent the actual data point of MW pixel counts. Since AD mostly happens in elderly individuals, the age range of control group and AD patients are different. This range for control group covers 20–100 years while for AD is 60–100 years. The trend related to control group in first years increased and then started to decrease. In fact, control and AD brains showed inverse non-linear patterns with age. Healthy brains trend indicated a slight increment from young to middle age and slighter decrease to the old, however, the AD brains had always decreased. The correlation of WM and age in control and AD groups were −0.35 and −0.5 respectively. Higher correlation of WM pixel counts with age was found in AD group.

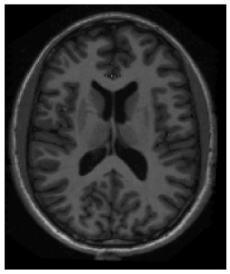
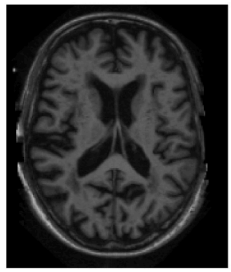
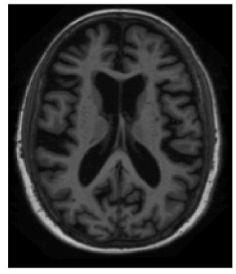
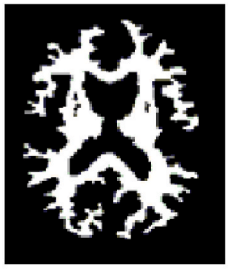
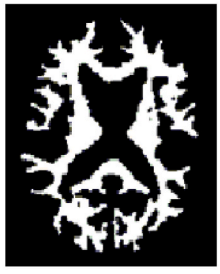
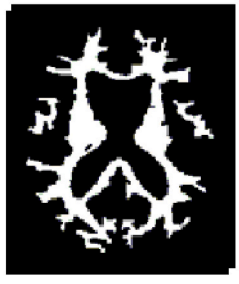
stages	Stage 1: Healthy	Stage 2: Very Mild AD	Stage 3: Mild AD
MR image			
EXTRACTED WM			
CDR	0	0.5	1

Fig. 2. The results of the artificial intelligence system for three individuals with three different levels of health including healthy brain (first column), very mild AD (scond column) and mild AD (third column). First raw: one slice of the magnetic resonance imaging (MRI), Second row: extracted white matter (WM) by the proposed AI system, third row: the value of clinical dementia rating (CDR) for each individual.

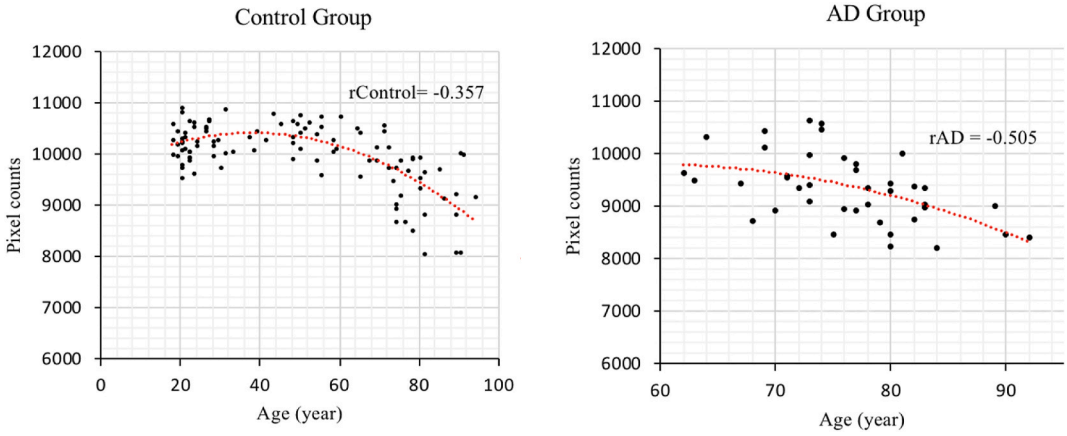


Fig. 3. The black point for each participant in their age group indicates the number of pixels (pixel count) of the retrieved white matter. The trend of pixel count with age is depicted by the red line (right: AD group, left: control group). The control group's Spearman's correlation coefficient is −0.357, with a p-value of 0.0001, whereas the Alzheimer's disease (AD) group's is −0.505, with a p-value of 0.0007.

4. Discussion

This work employed voxel-based morphometry and MRI to segment WM in the human brain. Furthermore, it accurately assessed normal ageing and AD in the segmented parts using pixel count in MRI. Fig. 3 showed the results of the age-related variation of WM in both control and AD groups.

Recent studies of age-related alterations have primarily focused on healthy brains. They have found conflicting results between ageing and WM changes; some have reported that WM decreases with age in the frontal, optic radiation, posterior [9] and anterior [4,32] limbs of the internal capsule, ventrolateral thalamus [9], and anterior colpus collasum [11], while others have not [14,32,33].

Some studies used MRI to study age-related changes in WM in normal adults, and their findings revealed non-linear changing

patterns with age [34,35]. According to our findings (Fig. 3), the control group's tendency confirmed that WM variations have a non-linear shift as they go from young to middle age and subsequently decrease as they age. The WM trend was entirely in line with the findings of earlier investigations [4,9]. In the AD group, WM changes with ageing were noticeable throughout adolescence. The findings of WM pixel count in AD patients were similar with prior data and support one of our initial hypotheses of reduced WM in AD. The Spearman's correlation coefficient was used to analyze the relationship between WM and the severity of dementia as a function of age.

The WM change with aging was more correlated in AD group ($rAD = -0.505$, p-value $= 0.0007$) than control group ($rControl = -0.357$, p-value $= 0.0001$). The results obtained for controls appeared to be consistent with those of another study on 84 normal persons aged 13–70 years [36]. A higher value of correlation (rAD) indicates that severity of the current state of the AD may influence age-related WM decline. This also suggests that, in addition to GM, WM is a cognitive change in AD, which contradicts the fact that AD has traditionally been considered as a GM disease. Few studies on the association between age, normal cognition, and brain morphology [33–38] found that reduction of both GM and WM volumes was involved in age-related cognitive alterations.

Recent studies [39,40] showed that age-related distractibility is possibly caused by impaired sensory gating by the locus coeruleus and insufficient top-down control by the frontal areas.

Regarding AD groups, we do not have exact histological proof; we can only conclude based on the findings of our study (Fig. 3) that WM pixel counts decline with age. Nonetheless, age-related abnormalities such as myelin degradation and the amount of myelinated fibre lengths may play a role [9]. As a result, these abnormalities could be caused by aging or by the residual effects of brain dementia.

4.1. Limitations

This study has provided the results about the mechanism of age-related change of brain during AD. It is limited, however, by lack of follow-up dataset for each group. other limitations of this study are the unequal number of female and male, and imaging protocol artifacts of the dataset. Further research endeavors should aim to consider these to provide better insight of age-related brain changes in the AD.

5. Conclusion

Our study presented an accurate standardization of MRI method for assessing WM alterations during brain dementia despite the previous studies that mostly employed the same techniques for both GM and WM volumetric evaluations. In addition, the majority of prior studies only looked at certain areas of WM in healthy brains, which may not be useful for assessing WM changes, especially in dementia patients. We picked full brain images based on a published study's recommendation [9], which said that in order to have a better knowledge of the pathological alterations of neurological disorders, entire brain images are desirable [9]. The global consideration of WM instead of regional provided an overall approach to detect age-related brain changes in both groups. In this study, higher correlation of WM pixel counts with age approved that AD is characterized by the relevant involvement of the WM and aging. Most of the studies about aging and AD were single-site or using relatively small sample sizes [4,41–43], our dataset, which included both healthy subjects and AD patients, enabled us to overcome this limitation. In order to develop and leverage this method for individuals with AD, research needs to use a representative sample of equal amounts of men and women.

Funding information

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Vania Karami: Writing – original draft, Software, Methodology, Data analysis. **Giovanna Ricci:** Writing – review & editing, Resources. **Giuliano Pesel:** Writing – review & editing, Software, Investigation. **Giulio Nittari:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Data of this study were provided by OASIS; OASIS Cross-Sectional: Principal Investigators: D. Marcus, R, Buckner, J, Csernansky J. Morris; P50 AG05681, P01 AG03991, P01 AG026276, R01 AG021910, P20 MH071616, U24 RR021382.

References

[1] E.D. Huey, J. Hardy, S.W. Scholz, B.J. Traynor, S.A. Small, Neurobiology of dementia and other neurodegenerative disorders, in: A. Tasman, et al. (Eds.), Tasman's Psychiatry, Springer, Cham, 2023, https://doi.org/10.1007/978-3-030-42825-9_60-1.

[2] P. Scheltens, K. Blennow, M.M. Breteler, B. de Strooper, G.B. Frisoni, S. Salloway, W.M. Van der Flier, Alzheimer's disease, Lancet 388 (10043) (2016 Jul 30) 505–517, https://doi.org/10.1016/S0140-6736(15)01124-1. Epub 2016 Feb 24.

[3] P. Londzin, M. Zamora, B. Kąkol, A. Taborek, J. Folwarczna, Potential of caffeine in Alzheimer's disease-A review of experimental studies, Nutrients 13 (2) (Feb 6 2021), https://doi.org/10.3390/nu13020537 (in eng).

[4] A. Giorgio, L. Santelli, V. Tomassini, R. Bosnell, S. Smith, N. De Stefano, H. Johansen-berg, Age-related changes in grey and white matter structure throughout adulthood, Neuroimage 51 (2010) 943–995, https://doi.org/10.1016/j.neuroimage.2010.03.004.

[5] M. Li, K.G. Schilling, F. Gao, L. Xu, S. Choi, Y. Gao, Z. Zu, A.W. Anderson, Z. Ding, B.A. Landman, J.C. Gore, Quantification of mediation effects of white matter functional characteristics on cognitive decline in aging, Cerebr. Cortex 34 (3) (2024) bhae114.

[6] R. Pedersen, L. Geerligs, M. Andersson, T. Gorbach, B. Avelar-Pereira, A. Wåhlin, A. Rieckmann, L. Nyberg, A. Salami, When functional blurring becomes deleterious: reduced system segregation is associated with less white matter integrity and cognitive decline in aging, Neuroimage 242 (2021) 118449.

[7] J.H. Kang, J.H. Bae, Y.J. Jeon, Age-related characteristics of resting-state electroencephalographic signals and the corresponding analytic approaches: a review, Bioengineering (Basel, Switzerland) 11 (5) (2024) 418.

[8] J.S.X. Chong, K.K. Ng, J. Tandi, C. Wang, J.H. Poh, J.C. Lo, M.W.L. Chee, J.H. Zhou, Longitudinal changes in the cerebral cortex functional organization of healthy elderly, J. Neurosci. : the official journal of the Society for Neuroscience 39 (28) (2019) 5534–5550.

[9] E.R. Sowell, P.M. Thompson, A.W. Toga, Mapping changes in the human cortex throughout the span of life, Neuroscientist 10 (2004) 372–392.

[10] N. Raz, K.M. Rodrigue, Differential aging of the brain: patterns, cognitive correlates and modifiers, Neurosci. Biobehav. Rev. 30 (2006) 730–748.

[11] D. Terribilli, S. Schaufelberger M, L.S. Duran Fabio, M.V. Zanetti, P. Curiati, R. Menezes P, M. Scazufca, Jr E. Amaro, C. C. Leite, F. Busatto G, Age-related gray matter volume changes in the brain during non-elderly adulthood, Neurobiol. Aging 32 (2011) (2009) 354–368, https://doi.org/10.1016/j.neurobiolaging.2009.02.008.

[12] F. Farokhian, C. Yang, I. Beheshti, H. Matsuda, S. Wu, Age-related gray and white matter changes in normal adult brains, Aging and disease 8 (6) (2017) 899–909, https://doi.org/10.14336/AD.2017.0502.

[13] L.C. Silbert, D. Lahna, N.O. Promjunyakul, et al., Risk factors associated with cortical thickness and white matter hyperintensities in dementia free okinawan elderly, J Alzheimers Dis (2018), https://doi.org/10.3233/JAD-171153.

[14] K.B. Walhovd, A.M. Fjell, I. Reinvang, A. Lundervold, A.M. Dale, D.E. Eilertsen, B.T. Quinn, D. Salat, N. Makris, B. Fischl, Effects of age on volumes of cortex, white matter and subcortical structures, Neurobiol. Aging 26 (2005) 1261–1270.

[15] A.F. Fotenos, A.Z. Snyder, L.E. Girton, J.C. Morris, R.L. Buckner, Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD, Neurology 64 (2005) 1032–1039.

[16] J.S. Allen, J. Bruss, C.K. Brown, H. Damasio, Normal neuroanatomical variation due to age: the major lobes and a parcellation of the temporal region, Neurobiol. Aging 26 (2005) 1245–1260.

[17] Y. Ge, R.I. Grossman, J.S. Babb, M.L. Rabin, L.J. Mannon, D.L. Kolson, Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis, AJNR Am. J. Neuroradiol 23 (2002) 1327–1333.

[18] Vania Karami, Giulio Nittari, Sara Karami, Seyed Massood Nabavi, Overview on incorporating computer-aided diagnosis systems for dementia, Exploring Future Opportunities of Brain-Inspired Artificial Intelligence (2023) 67–83, https://doi.org/10.4018/978-1-6684-6980-4.ch005.

[19] Jiayi Cai, Jialiang Cai, Deep neural network-based (BMI) brain-computer interface system design : development and evaluation of a BMI brain-computer interface learning framework for rehabilitation. 2023 International Conference on Computers, Information Processing and Advanced Education (CIPAE), 2023, pp. 423–427, https://doi.org/10.1109/CIPAE60493.2023.00087.

[20] V. Karami, G. Nittari, F. Amenta, Neuroimaging computer-aided diagnosis systems for Alzheimer's disease, Int J Imaging Syst Technol 29 (2019) 83–94, https://doi.org/10.1002/ima.22300.

[21] V. Karami, G. Nittari, E. Traini, F. Amenta, An optimized decision tree with genetic algorithm rule-based approach to reveal the brain's changes during Alzheimer's disease dementia, J Alzheimers Dis 84 (4) (2021) 1577–1584, https://doi.org/10.3233/JAD-210626.

[22] F.M.M. Gunning-Dixon, A. Brickman, C. Cheng J, S. Alexopoulos G, Aging of cerebral white matter: a review of MRI findings, Int J Geriatr Psychiatry 24 (2) (2009) 109–117, https://doi.org/10.1002/gps.2087.

[23] D.S. Marcus, T.H. Wang, J. Parker, J.G. Csernansky, J.C. Morris, R.L. Buckner, Open Access Series of Imaging Studies (OASIS): cross-sectional MRI data in young, middle aged, nondemented, and demented older adults, J Cogn Neurosci 19 (2007) 1498–1507.

[24] J. Barnes, B.C. Dickerson, C. Frost, L.C. Jiskoot, D. Wolk, W.M. van der Flier, Alzheimer's disease first symptoms are age dependent: evidence from the NACC dataset, Alzheimers Dement 11 (11) (2015) 1349–1357, https://doi.org/10.1016/j.jalz.2014.12.007.

[25] A. Shahbahrami, Algorithms and architectures for 2D discrete wavelet transform, J. Supercomput. 62 (2012) 1045–1064, https://doi.org/10.1007/s11227-012-0790-x.

[26] D.R. Nayak, R. Dash, B. Majhi, Brain MR Image Classification Using Two-Dimensional Discrete Wavelet Transform and Adaboost with Random Forests Neurocomputing, vol. 177, 2016, pp. 188–197.

[27] R. Vidal, Y. Ma, S.S. Sastry, Generalized Principal Component Analysis, Springer, New York, 2016, https://doi.org/10.1007/978-0-387-87811-9.

[28] T.A.F. Gomes, R.B.C. Prudêncio, C. Soares, A.L.D. Rossi, A. Carvalho, Combining meta-learning and search techniques to select parameters for support vector machines, Neurocomputing 75 (2012) 3–13.

[29] D.N.H. Thanh, et al., Blood vessels segmentation method for retinal fundus images based on adaptive principal curvature and image derivative operators, ISPRS - International Archives of the Photogrammetry, Remote Sensing and Spatial Information Sciences (May 2019) 211–218, https://doi.org/10.5194/isprs-archives-xlii-2-w12-211-2019. XLII-2/W12, Copernicus GmbH.

[30] M. Dessouky, M.A. Elrashidy, E.T. Taha, H.M. Abdelkader, Feature extraction of AD using different proposed algorithms, in: Book: Alzheimer's Disease, vol. 11, Publisher, 2017, p. 39. Chapter, http://www.smgebooks.com/alzheimers-disease/index.php.

[31] K. Okoye, S. Hosseini, Correlation tests in R: pearson cor, kendall's tau, and spearman's rho, in: R Programming, Springer, Singapore, 2024, https://doi.org/10.1007/978-981-97-3385-9_12.

[32] H. Watanabe, E. Bagarinao, S. Maesawa, et al., Characteristics of neural network changes in normal aging and early dementia, Front. Aging Neurosci. 13 (2021) 747359, https://doi.org/10.3389/fnagi.2021.747359. Published 2021 Nov 22.

[33] A.M. Brickman, C. Habeck, E. Zarahn, J. Flynn, Y. Stern, Structural MRI covariance patterns associated with normal aging and neuropsychological functioning, Neurobiol. Aging 28 (2007) 284–295.

[34] E.R. Sowell, B.S. Peterson, P.M. Thompson, S.E. Welcome, A.L. Henkenius, A.W. Toga, Mapping cortical change across the human life span, Nat. Neurosci. 6 (2003) 309–315.

[35] K.B. Walhovd, A.M. Fjell, I. Reinvang, A. Lundervold, A.M. Dale, D.E. Eilertsen, B.T. Quinn, D. Salat, N. Makris, B. Fischl, Effects of age on volumes of cortex, white matter and subcortical structures, Neurobiol. Aging 26 (2005) 1261–1270.

[36] E. Pagani, F. Agosta, M.A. Rocca, D. Caputo, M. Filippi, Voxel-based analysis derived from fractional anisotropy images of white matter volume changes with aging, Neuroimage 41 (2008) 657–667.

[37] A.M. MacLullich, K.J. Ferguson, I.J. Deary, J.R. Seckl, J.M. Starr, J.M. Wardlaw, Intracranial capacity and brain volumes are associated with cognition in healthy elderly men, Neurology 59 (2002) 169–174.

[38] C. Van Petten, E. Plante, P.S. Davidson, T.Y. Kuo, L. Bajuscak, E.L. Glisky, Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyper- intensities, Neuropsychologia 42 (2004) 1313–1335.

[39] I. Song, J. Neal, T.H. Lee, Age-related intrinsic functional connectivity changes of locus coeruleus from childhood to older adults, Brain Sci. 11 (11) (2021) 1485, https://doi.org/10.3390/brainsci11111485. Published 2021 Nov 10.
[40] T.H. Lee, S.H. Kim, B. Katz, M. Mather, The decline in intrinsic connectivity between the salience network and locus coeruleus in older adults: implications for distractibility, Front. Aging Neurosci. 12 (2020) 2, https://doi.org/10.3389/fnagi.2020.00002. Published 2020 Jan 31.
[41] S. Farahibozorg S M, J. Hashemi-Golpayegani, Ashburner, age- and sex-related variations in the brain white matter fractal dimension throughout adulthood: an MRI study, Clin. Neuroradiol. 25 (2015) 19–32, https://doi.org/10.1007/s00062-013-0273-3.
[42] Z. Arvanitakis, A. Fleischman D, K. Arfanakis, E. Leurgans S, L. Barnes L, A. Bennett D, Association of white matter hyperintensities and gray matter volume with cognition in older individuals without cognitive impairment, Brain Struct. Funct. 221 (2016) 2135–2146, https://doi.org/10.1007/s00429-015-1034-7.
[43] M. Mie Matsui, C. Tanaka, L. Niu, K. Noguchi, B. Bilker W, M. Wierzbicki, C. Gur R, Age-related volumetric changes of prefrontal gray and white matter from healthy infancy to adulthood, International Journal of Clinical and Experimental Neurology 4 (1) (2016) 1–8, https://doi.org/10.12691/ijcen-4-1-1.