Araştırma Makalesi
Research Article

White Matter Alterations In Amnestic Mild Cognitive Impairment: A Tract-Based Spatial Statistics Study

AMNESTİK HAFİF KOGNİTİF BOZUKLUKTA BEYAZ CEVHER DEĞİŞİKLİKLERİ: YOLAK TABANLI UZAMSAL İSTATİSTİK ÇALIŞMASI

Berrin ÇAVUŞOĞLU[1], Emel ADA[2], Derya Durusu EMEK SAVAŞ[3], Görsev YENER[4,5,6]

[1] DEÜ Sağlık Bilimleri Enstitüsü, Medikal Fizik Anabilim Dalı İzmir, Türkiye
[2] DEÜ Tıp Fakültesi Radyoloji Anabilim Dalı, İzmir, Türkiye
[3] DEÜ Edebiyat Fakültesi Psikoloji Bölümü,İzmir, Türkiye
[4,5,6] İzmir Ekonomi Üniversitesi Tıp Fakültesi, DEÜ Beyin Dinamiği Multidisipliner Araştırma ve Uygulama Merkezi, İzmir Biyotıp Ve Genom Merkezi ,İzmir, Türkiye

ABSTRACT

Purpose: To compare white matter (WM) structural alterations between the subjects with amnestic mild cognitive impairment (MCI) which is a transitional state to Alzheimer's Disease (AD) and healthy elderly controls.

Methods: Diffusion tensor imaging (DTI) scans of 20 subjects with amnestic MCI and 20 healthy control groups who are matched by age, gender, and education with the MCI group between 2011 and 2016 were examined by in this retrospective study. WM structural integrity was analyzed using tract-based spatial statistics (TBSS) for voxel-based differences in fractional anisotropy (FA) between the two groups.

Results: Fractional anisotropy was found significantly lower in the forceps minor, the body and genu of the corpus callosum, the right anterior thalamic radiation, the right cingulum, the right inferior fronto-occipital fasciculus, the right superior longitudinal fasciculus, and the right superior corona radiata in the MCI group than the control group.

Conclusion: TBSS analysis is a promising method to examine structural WM integrity. These findings suggested that the DTI measurements may be useful for the detection of preclinical changes in AD.

Keywords: Mild cognitive impairment, magnetic resonance imaging, diffusion tensor imaging, tract- based spatial statistics, fractional anisotropy

ÖZ

Amaç: Alzheimer Hastalığı'na geçiş durumu olan amnestik hafif kognitif bozukluğu (HKB) olan olgular ile sağlıklı yaşlı kontroller arasındaki beyaz cevher yapısal değişikliklerini karşılaştırmaktır.

Berrin ÇAVUŞOĞLU
DEÜ Sağlık Bilimleri Enstitüsü, Medikal Fizik Anabilim Dalı, İzmir, Türkiye
E-posta: berrncavusoglu@gmail.com.tr
https://orcid.org/0000-0003-1997-8861

DEU Tıp Derg 2022;36(3): 267-274
J DEU Med 2022;36(3):267-274
doi: 10.18614/deutip.1135057

Gönderim tarihi / Submitted: 23.06.2022
Kabul tarihi / Accepted: 20.12.2022

Gereç ve Yöntem: Bu retrospektif çalışmada, 20 amnestik HKB ile yaş, cinsiyet ve eğitim açısından HKB grubu ile eşleştirilmiş 20 sağlıklı kontrol grubunun 2011-2016 arasındaki difüzyon tensör görüntüleme (DTG) taramaları incelendi. Beyaz cevher yapısal bütünlüğü, iki grup arasındaki fraksiyonel anizotropide (FA) voksel bazlı farklılıklar için yolak tabanlı uzamsal istatistik (TBSS) kullanılarak analiz edildi.

Bulgular: Forseps minör, korpus kallozumun genu ve gövdesi, sağ anterior talamik radyasyon, sağ singulum, sağ inferior fronto oksipital fasikül, sağ superior longitudinal fasikül ve sağ üst korona radiatada FA değerleri kontrol grubuna göre HKB grubunda istatistiksel olarak düşük bulundu.

Sonuç: TBSS analizi, yapısal beyaz cevher bütünlüğünü incelemek için umut verici bir yöntemdir. Bu bulgular, DTG ölçümlerinin Alzheimer'daki klinik öncesi değişikliklerin saptanması için yararlı olabileceğini düşündürdü.

Anahtar Kelimeler: Hafif kognitif bozukluk, manyetik rezonans görüntüleme, difüzyon tensör görüntüleme, yolak tabanlı uzamsal istatistik, fraksiyonel anizotropi

Alzheimer's disease (AD) is the most common form of dementia and is related to progressive decline in memory and other cognitive functions. AD is defined by the presence of senile plaques and neurofibrillary tangles, which both occur with neuronal cell death and structural atrophy of the subcortical and cortical structures in the brain (1, 2). Amnestic mild cognitive impairment (MCI) is considered a state of transition from normal aging to AD and has a higher conversion rate, 15–20% per year, than the general population (2, 3). Recent research suggests that pathophysiological changes related to AD start 10–25 years before symptoms of dementia start (2-4). Therefore, identifying biomarkers is very important for diagnosing AD in the preclinical and early stages of the disease.

AD has been treated as a disease of gray matter (GM) with white matter (WM) degeneration as a secondary effect. Magnetic resonance imaging (MRI) studies have found that in AD, GM atrophy starts in the limbic areas and medial temporal and spreads to the parietal, frontal, and primary cortices (5). Although WM degeneration has been demonstrated in AD patients, the mechanisms are not well understood (6).

To show structural WM integrity, diffusion tensor imaging (DTI) has been extensively used. Loss of WM integrity is indicated by diminishing fractional anisotropy (FA), which is the extent of directionality of water diffusion in the WM tracts. Tract-Based Spatial Statistics (TBSS) is an observer-independent, fully automated tract-based approach for the voxel-wise analysis of the FA values in the major WM tracts, which allows for group comparisons (7). Lower FA values were reported for patients with AD. WM abnormalities have been shown in multiple fiber tracts in the parietal, frontal, and temporal lobes (8). Moreover, some studies have shown WM differences in MCI patients. However, inconsistent findings were noted in a few studies that have investigated structural WM degeneration in MCI patients.

In this study, WM structural differences in the amnestic MCI period were investigated compared to controls using the TBSS. We attempted to assess the hypothesis that FA values would be reduced in MCI patients relative to healthy controls.

MATERIALS AND METHOD

Participants

This study was carried out retrospectively between 2011-2016 including 20 subjects with amnestic MCI (mean age 74.45±5.58 years), which were evaluated using the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria (3). The control group (mean age 72.45 ± 5.73 years) included 20 healthy elderly volunteers matched with the MCI group by age, gender, and education.

All participants underwent conventional brain MRI and diffusion tensor imaging. A comprehensive

neuropsychological test battery including Mini-Mental State Examination (MMSE) (9) and Clinical Dementia Rating Scale (CDR) (10) was performed on all participants by the neurologists.

For healthy elderly participants, the inclusion criteria were no cognitive deficits and/or neurological abnormality (MMSE score ≥ 27). For patients with MCI, the inclusion criteria were (i) memory impairments identified with performances ≥ 1.5 standard deviation below for age- and education-matched controls in a battery of neuropsychological tests, accompanied by no impairment of daily living activities, (ii) having a CDR score of 0.5. The exclusion criteria for MCI and healthy controls were as follows: (i) history of neurological and/or psychiatric diseases, (ii) presence of vascular brain lesions or tumors, (iii) other causes for cognitive impairment including head injury, alcohol, and/or drug abuse, and (iv) use of psychoactive drugs or cognitive enhancers.

Group characteristics are shown in Table 1. There was no difference in distributions of age, gender, or education between MCI patients and controls. This study was approved by the local ethical committee.

Table 1 Demographic and clinical characteristics of participants

	Healthy Controls (n=20)	MCI (n=20)	p
Age(yr)	72.45 (5.73)	74.45 (5.58)	0.279[a]
Gender (M/F)	10/10	10/10	1.000[b]
Education (yr)	10.60 (5.25)	9.65 (3.84)	0.311[a]
MMSE	29.35 (0.93)	22.20 (10.01)	<0.001[a]

MCI, mild cognitive impairment; MMSE, the Mini-Mental State Examination; M, Male; F, Female; aMann-Whitney U Test, [b]Chi Square

Magnetic resonance imaging

MR imaging was acquired by a 1.5 Tesla Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands). DTI scans were performed using gradient echo single shot EPI sequence (TR: 3464 ms, TE: 90 ms, FOV: 230, matrix: 112×128, slice thickness: 5 mm with 24 axial slices) with diffusion gradients (b values 0 and 1000 s/mm^2) applied in 6 directions.

TBSS Analysis

DTI processing was conducted using tract-based spatial statistics (TBSS) in FSL (FMRIB Software Library; version 6.0; www.fmrib.ox.ac.uk/fsl) (11). DTI images were corrected for eddy currents and motion and aligned to the b0 image using an affine transformation.

FA was calculated with the DTIFIT algorithm (FMRIB Software Library's Diffusion Toolbox). FA maps were processed using TBSS voxel-wise statistical analysis. All individual FA maps were aligned into a standard space MNI152 template. A mean white matter skeleton was generated from the mean FA map and was thresholded by a FA value of 0.2.

Statistical Analysis

Comparisons of demographic and clinical variables between groups were using the chi-square test or Mann–Whitney U via the SPSS version 24.0 (IBM; Armonk, NY, USA). $p<0.05$ was considered statistically significant. A nonparametric permutation test (12) was used for TBSS group comparisons of individual FA skeletons between MCI and controls in FSL. The number of random

permutations was set at 5000, and the significance level was set at p<0.05. The threshold-free cluster enhancement (TFCE) method (13) was used for multiple comparison corrections. Abnormal WM tracts were identified according to the atlas formulated at Johns Hopkins University, which is available within FSL (14).

RESULTS

TBSS exhibited significantly lower FA in the MCI group relative to the controls in the corpus callosum (body and genu), forceps minor, right anterior thalamic radiation, right cingulum, right inferior fronto-occipital fasciculus, right superior corona radiata, and also in the right superior longitudinal fasciculus (Figure 1 and Table 2).

Figure 1. TBSS results of FA maps between MCI and healthy controls. Regions that showed reduced FA values in MCI compared to controls have been highlighted in red-yellow colors (p<0.05, corrected for multiple comparisons)

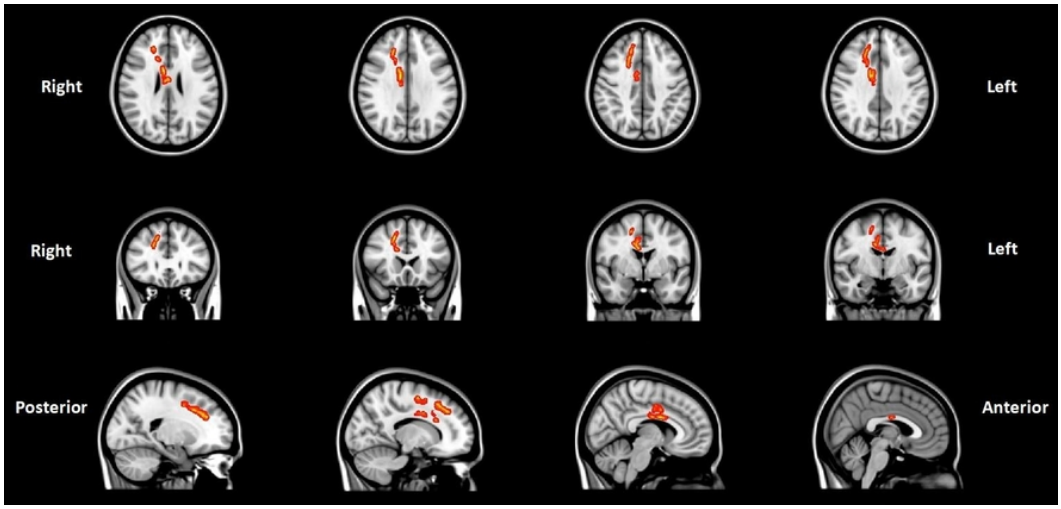

Table 2 Anatomic locations showing significantly (p < 0.05, TFCE-corrected) reduced FA on TBSS Analysis

Brain region	Cluster size (voxels)	P-value (TFCE)	MNI coordinates of the peak voxel		
			x	y	z
Right superior longitudinal fasciculus, right inferior fronto-occipital fasciculus, forceps minor, right anterior thalamic radiation, right superior corona radiata, the body of corpus callosum	568	0.041	16	24	45
Right cingulum, the body of the corpus callosum	428	0.038	10	4	28
Right cingulum, right inferior fronto-occipital fasciculus	155	0.047	19	4	45
The body of corpus callosum	82	0.049	4	-10	25
The genu of the corpus callosum, right cingulum	36	0.049	15	20	24

TBSS = tract-based spatial statistics; TFCE = threshold-free cluster-enhancement; MNI = Montreal Neurological Institute

DISCUSSION

DTI has been commonly used to examine the structural integrity of WM cerebral connections in MCI. Whole-brain DTI analysis offers higher accuracy for WM comparisons between subjects and is preferred over the conventional region of interest (ROI) method. One of the most utilized methods is TBSS, which overcomes ROI's limitations (15, 16), including variance effects and tract misalignment in brain atrophy, and partial volume estimations (17). While AD is believed to be more closely linked to neuronal damage, there is evidence that dendritic and axonal atrophy is followed by neuronal death in this disease (18). Lower FA values indicate a loss of WM integrity. In our study, significantly reduced FA values were observed in MCI patients in several major WM tracts, like forceps minor, cingulum, corpus callosum, inferior fronto-occipital fasciculus, superior corona radiate, superior longitudinal fasciculus, and anterior thalamic radiation on the right hemisphere.

Recent TBSS studies have had conflicting results on WM changes in MCI patients. Several studies did not report any significant FA difference between MCI patients and controls (15,19-25), whereas others exhibited lower FA values in MCI patients (7, 26-30). These lower values were in long interhemispheric and intrahemispheric WM tracts like the corpus callosum, its association fibers (26), and the temporal (26, 27), frontal, and parietal lobes (26-28). Inconsistencies between these studies could be due to differences in sample sizes, imaging protocols (field strength, number of directions, and b value), MCI diagnostic criteria, or heterogeneous groups of subjects (converters/non-converters, early/late, single/multi-domain). Furthermore, in another TBSS study, Haller et al. (2010) found significantly lower FA values in MCI compared to controls in a large distributed network (31). This was most marked in the right frontal and temporal WM pathways and the corpus callosum. The findings of our study corroborate these findings, except for the temporal WM tracts.

Earlier studies revealed that the spread of AD pathology reflects the reverse myelination pattern, a phenomenon referred to as retrogenesis (32). It was shown that later myelinated brain areas, like the temporal and frontal lobes, are most vulnerable before early myelinating areas (33). In this line, WM pathways of the frontal lobe and corpus callosum could be considered as a late-myelinating region. This could help explain our findings regarding the reduction in FA values in these regions and our findings provide qualitative support for the vulnerability of late-myelinating areas, particularly at the earlier stages of AD. We may speculate that dysfunction of WM tracts in these areas can affect myelin integrity. Therefore, they may be involved with the pathogenesis of AD.

In MCI, reduced FA was identified in pathways connecting atrophic GM regions involving disrupted brain networks in AD. The impaired WM pathways are anatomically connected to amyloid-affected regions in AD included: forceps minor, connecting the bilateral prefrontal cortex; anterior thalamic radiation, connecting the prefrontal cortex with the thalamus; cingulum, connecting the cingulate cortex with the entorhinal cortex; inferior fronto-occipital fasciculus, connecting the parietal and occipital lobes with frontal lobe; superior longitudinal fasciculus, connecting bilateral temporal and frontal lobe with parietal lobe; corpus callosum, connecting frontal lobe with parietal and temporal lobes; superior corona radiata, connecting temporal lobe, parietal lobe, and corpus striatum. Furthermore, most of the mentioned WM pathways linking these major cortical hubs of cognitive networks are in the default mode network (DMN), which was found to be disrupted in MCI. (34-37). Therefore, it may be speculated that the abnormalities in the major WM tracts may responsible for the disruption of communication among DMN components.

This study has certain limits. Firstly, the number of subjects participating in this study is limited. Secondly, this is a cross-sectional study which does not allow us to follow changes over time. A follow-up study is required to identify longitudinal alterations in predicting the progression from MCI to AD. Third, our DTI data is only six directional with a 5 mm thick slice. Therefore, changes in FA values less than 5 mm cannot be reliably evaluated in small tracts (e.g., the fornix). Perhaps that influenced our results. Another limitation is that we did not separate MCI patients into subtypes, which could have affected the

results. Reproducing these findings in an MCI cohort that later develops into AD would help confirm that results represent a pattern of Alzheimer's type pathologic change expected early.

In conclusion, decreased FA in subjects with MCI compared with controls could be a marker of disease related to cognitive impairment. Therefore, we suggest that DTI measurements can be a helpful marker to detect preclinical changes in AD. Longitudinal studies are required in patients with MCI to reveal the inconsistencies between cross-sectional studies and other studies that should be carried out with the morphometric characteristics of WM.

REFERENCES

1. Singh SK, Srivastav S, Yadav AK, Srikrishna S, Perry G. Overview of Alzheimer's Disease and Some Therapeutic Approaches Targeting Aβ by Using Several Synthetic and Herbal Compounds. Oxid Med Cell Longev, 2016;2016:7361613.
2. Defrancesco M, Egger K, Marksteiner J, Esterhammer R, Hinterhuber H, Deisenhammer EA, et al. Changes in White Matter Integrity before Conversion from Mild Cognitive Impairment to Alzheimer's Disease. PLoS One, 2014;9:e106062.
3. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement, 2011;7:270-9.
4. Clark CM, Pontecorvo MJ, Beach TG, Bedell BJ, Coleman RE, Doraiswamy PM, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. Lancet Neurol, 2012;11:669-78.
5. Westman E, Aguilar C, Muehlboeck JS, Simmons A. Regional magnetic resonance imaging measures for multivariate analysis in Alzheimer's disease and mild cognitive impairment. Brain Topogr, 2013;26:9-23.
6. Morris JK, Honea RA, Vidoni ED, Swerdlow RH, Burns JM. Is Alzheimer's disease a systemic disease? Biochim Biophys Acta, 2014;1842:1340-9.
7. Shu N, Wang Z, Qi Z, Li K, He Y. Multiple diffusion indices reveals white matter degeneration in Alzheimer's disease and mild cognitive impairment: a tract-based spatial statistics study. J Alzheimers Dis, 2011;26:275-85.
8. Agosta F, Pievani M, Sala S, Geroldi C, Galluzzi S, Frisoni GB, et al. White matter damage in Alzheimer disease and its relationship to gray matter atrophy. Radiology, 2011;258:853-63.
9. Folstein MF, Folstein SE, McHugh PR. ''Mini-mental state'': A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 1975;12(3):189-98.
10. Morris J. The clinical dementia rating (CDR): current version and scoring rules. Neurology, 1993;43:2412-4.
11. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage, 2006;31:1487-505.
12. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Human Brain Mapping, 2002;15:1-25.
13. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. NeuroImage, 2009;44:83-98.
14. Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. Radiology, 2004;230:77-87.
15. Bosch B, Arenaza-Urquijo EM, Rami L, Sala-Llonch R, Junqué C, Solé-Padullés C, et al. Multiple DTI index analysis in normal aging, amnestic MCI and AD. Relationship with neuropsychological performance. Neurobiol Aging, 2012;33:61-74.

16. Sexton CE, Kalu UG, Filippini N, Mackay CE, Ebmeier KP. A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging, 2011;32:2322.

17. Di Paola M, Di Iulio F, Cherubini A, Blundo C, Casini AR, Sancesario G, et al. When, where, and how the corpus callosum changes in MCI and AD: a multimodal MRI study. Neurology, 2010;74:1136-42.

18. Liu PP, Xie Y, Meng XY, Kang JS. History and progress of hypotheses and clinical trials for Alzheimer's disease. Signal Transduct Target Ther, 2019;4:29.

19. Damoiseaux JS, Smith SM, Witter MP, Sanz-Arigita EJ, Barkhof F, Scheltens P, et al. White Matter Tract Integrity in Aging and Alzheimer's Disease. Hum Brain Mapp, 2009;30:1051-9.

20. Douaud G, Jbabdi S, Behrens TEJ, Menke RA, Gass A, Monsch AU, et al. DTI measures in crossing-fibre areas: increased diffusion anisotropy reveals early white matter alteration in MCI and mild Alzheimer's disease. Neuroimage, 2011;55:880-90.

21. Lim HK, Kim SJ, Choi CG, JH Lee, Kim SY, Kimet HJ, al. Evaluation of White Matter Abnormality in Mild Alzheimer Disease and Mild Cognitive Impairment Using Diffusion Tensor Imaging: A Comparison of Tract-Based Spatial Statistics with Voxel-Based Morphometry. Journal of the Korean Society of Magnetic Resonance in Medicine, 2012; 16(2): 115-23.

22. Liu Y, Spulber G, Lehtimäki KK, Könönen M, Hallikainen I, Gröhn H, et al. Diffusion tensor imaging and tract-based spatial statistics in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging, 2011;32:1558-71.

23. Nir TM, Jahanshad N, Villalon-Reina JE, Toga AW, Jack CR, Weiner MW, et al. Effectiveness of regional DTI measures in distinguishing Alzheimer's disease, MCI, and normal aging. Neuroimage Clin, 2013;3:180-95.

24. Rowley J, Fonov V, Wu O, Eskildsen SF, Schoemaker D, Wu L, et al. White matter abnormalities and structural hippocampal disconnections in amnestic mild cognitive impairment and Alzheimer's disease. PLoS One, 2013;8:e74776.

25. O'Dwyer L, Lamberton F, Bokde ALW, Ewers M, Faluyi YO, Tanner C, et al. Multiple indices of diffusion identifies white matter damage in mild cognitive impairment and Alzheimer's disease. PLoS One, 2011;6:e21745.

26. Liu J, Yin C, Xia S, Jia L, Guo Y, Zhao Z, et al. White matter changes in patients with amnestic mild cognitive impairment detected by diffusion tensor imaging. PLoS One, 2013;8:e59440.

27. Zhuang L, Wen W, Zhu W, Trollor J, Kochan N, Crawford J, et al. White matter integrity in mild cognitive impairment: a tract-based spatial statistics study. Neuroimage, 2010;53:16-25.

28. Wai YY, Hsu WC, Fung HC, Lee JD, Chan HL, Tsai ML, et al. Tract-based spatial statistics: application to mild cognitive impairment. Biomed Res Int, 2014;2014:713079.

29. Wang Y, West JD, Flashman LA, Wishart HA, Santulli RB, Rabin LA, et al. Selective changes in white matter integrity in MCI and older adults with cognitive complaints. Biochim Biophys Acta, 2012;1822:423-30.

30. 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;6:734-46.

31. Haller S, Nguyen D, Rodriguez C, Emch J, Gold G, Bartsch A, et al. Individual prediction of cognitive decline in mild cognitive impairment using support vector machine-based analysis of diffusion tensor imaging data. J Alzheimers Dis, 2010;22:315-27.

32. Reisberg B, Franssen EH, Souren LEM, Auer SR, Akram I, Kenowsky S. Evidence and mechanisms of retrogenesis in Alzheimer's and other dementias: management and treatment import. Am J Alzheimers Dis Other Demen, 2002;17(4):202-12.

33. Nasrabady SE, Rizvi B, Goldman JE, Brickman AM. White matter changes in Alzheimer's disease:

a focus on myelin and oligodendrocytes. Acta Neuropathol Commun, 2018;6:22.

34. Qi Z, Wu X, Wang Z, Zhang N, Dong H, Yao L, et al. Impairment and compensation coexist in amnestic MCI default mode network. Neuroimage, 2010;50:48-55.

35. Rombouts SA, Barkhof F, Goekoop R, Stam CJ, Scheltens P. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. Human Brain Mapping, 2005;26:231-9.

36. Garcés P, Pineda-Pardo JA, Canuet L, Aurtenetxe S, López ME, Marcos A, et al. The Default Mode Network is functionally and structurally disrupted in amnestic mild cognitive impairment - a bimodal MEG-DTI study. Neuroimage Clin., 2014;6:214-21.

37. Wang CL, Pan Y, Liu YM, Xu K, Hao LX, Huang F, et al. Aberrant default mode network in amnestic mild cognitive impairment: a meta-analysis of independent component analysis studies. Neurol Sci., 2018;39(5):919-31.