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Clinical study

White-matter changes in early and late stages of mild cognitive impairment

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ABSTRACT

Mild Cognitive Impairment (MCI) is characterized by cognitive deficits that exceed age-related decline, but not interfering with daily living activities. Amnestic type of the disorder (aMCI) is known to have a high risk to progress to Alzheimer's Disease (AD), the most common type of dementia. Identification of very early structural changes in the brain related to the cognitive decline in MCI patients would further contribute to the understanding of the dementias. In the current study, we target to investigate whether the white-matter changes are related to structural changes, as well as the cognitive performance of MCI patients. Forty-nine MCI patients were classified as Early MCI (E-MCI, n = 24) and Late MCI (L-MCI, n = 25) due to their performance on The Free and Cued Selective Reminding Test (FCSRT). Age-Related White-Matter Changes (ARWMC) scale was used to evaluate the white-matter changes in the brain. Volumes of specific brain regions were calculated with the FreeSurfer program. Both group and correlation analyses were conducted to show if there was any association between white-matter hyperintensities (WMHs) and structural changes and cognitive performance. Our results indicate that, L-MCI patients had significantly more WMHs not in all but only in the frontal regions compared to E-MCI patients. Besides, ARWMC scores were not correlated with total hippocampal and white-matter volumes. It can be concluded that WMHs play an important role in MCI and cognitive functions are affected by white-matter changes of MCI patients, especially in the frontal regions.

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1. Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease mainly characterized by the accumulation of amyloid plaques and neurofibrillary tangles and is the most common form of all dementia disorders. Its prevalence is gradually increasing worldwide, and in 2050, AD is thought to increase four times the current number [1]. In the course of the disease, the majority of the patients presents subtle cognitive deficits in the initial phase. Both Subjective Cognitive Impairment (SCI) and Mild Cognitive Impairment (MCI) may represent a translational step between age-related problems and dementia. Nevertheless, MCI can also be seen in other conditions where neurodegeneration is not present. Even side effects of some medications, psychiatric disorders, sleep problems, and vascular diseases can be the cause of the cognitive problems in MCI patients [2]. For the best diagnosis and treatment, it is noteworthy to recognize if neurodegeneration is the underlying reason for dementia and cognitive problems.

MCI is diagnosed based on several criteria [3]. First of all, the person has to have cognitive complaints. Secondly, the cognitive performance should be 1.5 standard deviation (SD) below the subject's peers. Thirdly, there should be a normal performance of daily

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living activities in patients. MCI subdivided into four classes depending on memory complaints as amnestic and non-amnestic and the number of the impaired cognitive domains as single-domain, multiple-domain [4]. Amnestic MCI (aMCI) patients show memory deficits while non-amnestic (naMCI) MCI patients' memory is intact even they have cognitive impairment in other domains. It is shown that aMCI patients are more likely to convert from MCI to AD than naMCI patients [5].

White-matter hyperintensities (WMHs) could be best detected in magnetic resonance imaging (MRI), and their prevalence is found to be increased with age [6]. They may be seen in healthy people as well as in people with high vascular risk [7]. WMHs were found to be correlated with decreased performance in tasks on executive functions, episodic memory, and slower speed of processing in healthy older adults [8], which indicates that it might play a substantial role in cognitive processes.

WMHs can also be an indicator of the progression from MCI to AD [9]. In a follow-up study using Computer Tomography (CT) imaging, WMHs were found in the initial scans of 7 of 8 MCI patients who converted to dementia [10]. In another follow-up study using MRI, periventricular WMHs predicted conversion to dementia [11]. However, there are contradictory findings in the literature emphasizing no difference of WMHs presence between patients with dementia and healthy subjects [12]. WMHs were also found to be associated with conversion from a healthy sate to MCI but not to further dementia [13]. There is a need to understand the role of WMHs in the course of dementia, especially in patients with a high risk of developing AD.

In the current study, our first aim was to investigate whether the WMHs were related to the cognitive performance of MCI patients. Since there is an apparent correlation between cognitive performance and structural changes of the brain in dementia, our secondary aim was to evaluate the association between WMHs and structural changes seen in MCI patients and their relevance to cognitive impairment.

2. Materials and methods

2.1. Ethics

In the current study, data analyzed as part of a thesis project approved by Istanbul University, Istanbul Faculty of Medicine, Clinical Research Ethics Committee on 25/05/2018 in the meeting with the number of 10.

2.2. Clinical assessment

Data of 49 aMCI patients, consequently admitted to Istanbul University, Istanbul Faculty

of Medicine, Department of Neurology, Behavioral Neurology, and Movement Disorders Unit between 2014 and 2016, were analyzed. Clinic data of patients, including the scores of Mini-Mental State Examination test (MMSE), Clinical Dementia Rating (CDR), and The Free and Cued Selective Reminding Test (FCSRT) were obtained from the clinical file of the patients.

2.3. Classification of participants

The FCSRT, known to be sensitive to the early stages of dementia was used for the diagnosis of MCI and patients with a total score of < 35 on FCSRT free call measure were grouped as MCI [14]. For the subclassification of patients, median of FCSRT free recall score was used as a cut-off score. Patients who scored $\leq$ 26 were grouped as "Late MCI" (L-MCI), while others with a score of > 26 were grouped as Early MCI (E-MCI). The E-MCI group consisted of 24 patients, and there were 25 patients in the L-MCI group.

2.4. Magnetic resonance imaging acquisition

The 3 T magnetic resonance imaging system (Phillips, Achieva, Best, Holland) was used for data acquisition at Istanbul University, Hulusi Behcet Life Sciences Research Centre. For structural MRI, T1 and T2-weighted images were acquired using 32 channel SENSE head coil. 3D TFE (Turbo Field Echo) sequence was used to acquire T1-weighted images with the following parameters: Total scan time = 4 min 55 s, TR = 8.5 ms, TE = 3.9 ms, matrix = 220 $\times$ 240, number of axial slices = 180, thickness = 1 mm and voxel size = 1 $\times$ 1 $\times$ 1 mm3. T2-weighted images were acquired using MS (Multi Slice) TSE (Turbo Spin Echo) sequence with the following parameters: Total scan time = 1 min 41 s, TR = 8452 ms, TE = 80 ms, matrix = 104 $\times$ 120, number of axial slices = 90, thickness = 2 mm and voxel size = 2 $\times$ 2 $\times$ 2 mm3. Fluid Attenuated Inversion Recovery (FLAIR) scans were recorded with the following parameters: Total scan time = 52 s, TR = 4800 ms, TE = 259 ms, TI = 1650 ms, matrix = 224 $\times$ 224, number of axial slices = 60, and voxel size = 3 $\times$ 3 $\times$ 3 mm3.

2.5. Evaluation of the White-Matter changes

Axial FLAIR images were visually inspected and we used "Age-Related White Matter Changes" (ARWMC) scale in order to quantify the white-matter changes in MCI patients [15]. This scale measures white-matter changes based on a four-point system (0 = no lesions; 1 = focal lesions; 2 = beginning confluence of lesions and 3 = diffuse involvement) in ten regions (left and right regions as frontal, parieto-occipital, temporal, basal ganglia and infratentorial).

2.6. Volumetric measurements

Volumes of the hippocampus, cerebral white-matter, and cerebral cortex were computed using Freesurfer (stable v6.0 version http://surfer.nmr.mgh.harvard.edu). For the volumetric measurements, T1-weighted images were analyzed using an automatic "*recon-all*" stream with the completion of the following steps: motion correction, intensity normalization, skull-stripping, volumetric registrations, white and gray matter segmentation, spherical mapping, spherical registration and cortical parcellation. After the completion of *recon-all*, all images were visually inspected and minor manual editing was done if needed.

2.7. Statistical analysis

For all statistical analysis, Statistical Package for Social Sciences software (SPSS, version 20, https://www.ibm.com/analytics/spss-statistics-software) was used. For the analysis of ARWMC scores, Test of Normality results showed that the data were not normally distributed. So, we used the Mann-Whitney *U* test to compare the scores of the two groups. Multivariate Analysis of Covariance (MANCOVA) using total intracranial volume and age as covariates, was used to compare the volumetric analysis of the hippocampus, white-matter and cortex. Furthermore, we used Spearman's correlation test to analyze the relationship of brain volumes with ARWMC scores.

3. Results

Demographic data of patients was shown in Table 1. Age is found to be not significantly different between groups t

Table 1
Demographic information of Early and Late MCI patients.

	Early MCI	Late MCI
Age	56.79 (8.47)	59.44 (8.39)
Sex	24 (12F)	25 (16F)
Education	15.79 (3.95)	11.12 (5.15)
FCSRT Score	30.96 (3.26)	20.02 (3.97)
CDR-SB	0.15 (0.24)	0.76 (0.56)

FCSRT: The Free and Cued Selective Reminding Test free recall mean score;
CDR-SB: Clinical Dementia Rating Scale Sum of Boxes mean score.
Scores are given in mean (SD).

(47) = 1.10, p = 0.277. CDR-Sum of Boxes (CDR-SB) scores of L-MCI patients were found to be significantly higher than E-MCI patients t (44) = 4.80, p = 0.021.

Mann-Whitney *U* test results comparing ARWMC scores showed no statistically significant difference between two groups in parieto-occipital, temporal, basal ganglia and infratentorial regions (p > 0.05). However, L-MCI patients were found to have significantly more WM hyperintensities in the left frontal (U = 187, p = .011) and right frontal regions (U = 197, p = .022) compared to E-MCI patients. In addition, ARWMC total score was analyzed between groups and Mann-Whitney *U* test results show that there is a tendency of higher ARWMC scores of L-MCI patients than E-MCI group (U = 205, p = .053). Mean total score on ARWMC scale in each region can be found in Table 2.

The mean values of the volumes of the analyzed brain regions can be found in Table 3. MANCOVA results show that after controlling the effects of age and intracranial volume, volumes of the cortex, white-matter and hippocampus were not found to be significantly different between groups: right hippocampal volume F(1,45) = 0.400, p = .53; left hippocampal volume, F(1,45) = 0.005, p = .95, white-matter volume, F(1,45) = 0.249, p = .62 and total cortex volume, F(1,45) = 0.158, p = .69.

Table 2
Mean ARWMC scores of Early and Late MCI patients.

ARWMC	Early MCI	Late MCI	p-value
LF	0.46 (0.51)	0.96 (0.74)	0.011
RF	0.50 (0.60)	0.92 (0.64)	0.022
LPO	0.67 (0.76)	0.64 (0.91)	0.689
RPO	0.54 (0.78)	0.64 (0.91)	0.783
LT	0.00 (0.00)	0.16 (0.62)	0.162
RT	0.00 (0.00)	0.04 (0.2)	0.327
LBG	0.00 (0.00)	0.12 (0.6)	0.327
RBG	0.00 (0.00)	0.12 (0.6)	0.327
LINF	0.00 (0.00)	0.08 (0.26)	0.161
RINF	0.00 (0.00)	0.00 (0.00)	1000
Total ARWMC Score	2.17 (2.24)	3.68 (2.98)	0.053

LF: Left Frontal ARWMC score; RF: Right Frontal ARWMC score;
LPO: Left Parieto-Occipital ARWMC score; RPO: Right Parieto-Occipital ARWMC score;
LT: Left Temporal ARWMC score; RT: Right Temporal ARWMC score;
LBG: Left Basal Ganglia ARWMC score; RBG: Right Basal Gaglia ARWMC score;
LINF: Left Infratentorial ARWMC score; RINF: Right Infratentorial ARWMC score.
Scores are given in mean (SD).

Table 3
Mean left and right hippocampal, white-matter and total cortex volumes of Early and Late MCI patients (mm3).

Volume (mm3)	Early MCI	Late MCI	p-value
LH	3916.53 (342.75)	3978.47 (465.09)	0.862
RH	4149.82 (325.25)	4132.45 (468.46)	0.669
WM	477063.03 (53133.18)	493967.98 (67361.36)	0.521
TC	420259.67 (38579.91)	430451.42 (45351.83)	0.704

LH: Left hippocampus volume; RF: Right hippocampus volume;
WM: Cerebral white matter volume; TC: Total cortex volume.
Volumes are given in mean (SD).

Lastly, Spearman's correlation test results showed that none of the ARWMC scores in certain regions were significantly correlated with total hippocampal and white-matter volumes, p > 0.05. Correlation coefficients can be seen in Table 4.

4. Discussion

In the present study, the relationship between white-matter hyperintensities and cognitive performance in MCI patients was evaluated. MCI patients divided into two groups as late and early, based on their performance on an episodic memory test, and our findings show that L-MCI patients had significantly more white-matter hyperintensities in both left and right frontal regions compared to E-MCI patients. This result is compatible with the previous findings on white-matter changes. Several imaging studies found that patients had significantly more WMHs in frontal regions compared to other locations in patients with cognitive decline [16,17].

Frontal white-matter is involved in numerous cognitive functions as frontal white-matter connects the prefrontal cortex with various cortical and subcortical areas [18]. In a structural MRI study, researchers analyzed whether the cognitive performance was associated with subcortical or periventricular white-matter lesions, and they found global cognitive performance was associated with periventricular white-matter lesions [19]. In a *meta*-analysis, healthy participants' WMHs were found to be associated with worse cognitive performance, especially in executive functions, speed of processing, memory and global cognitive performance [7]. Our results confirmed the similar findings in the literature that frontal WMHs might play a role in cognitive functions, such as worse memory performance of MCI patients.

The presence of WMHs was also associated with an increased risk of dementia. In a MRI study, it was found that MCI patients who converted to AD in around 18 months had significantly lower scores on several memory tests and more WM hyperintensities than non-converters [20]. Both worse memory performance and presence of WMHs in MCI patients may be related to conversion to dementia in our cohort; however cross-sectional design of our study hinders this finding to be shown here.

Total cerebral cortex, total cerebral white-matter, and hippocampal volumes did not differ between groups when the effects of age and total intracranial volumes are controlled. In line with our findings, other studies found similar results that hippocampal volumes did not show any difference in patients with high risk to develop dementia. On the other hand, in a follow-up study, only parietal WMH volumes predicted the conversion to AD, while WMHs in other locations and hippocampal volumes failed to predict [21]. These findings might suggest that, in patients with high risk to develop dementia, disturbed memory performance might be related to WM changes rather than atrophy of the medial temporal lobe structures. Another explanation to the lack of hippocampal differences in our cohort may be related to the heterogeneous nature of MCI. There is a need for a biologically based diagnosis of MCI in order to represent the early stages of all kinds of dementia disorders.

As a limitation, our data did not include any methods showing the presence of tau and amyloid accumulation in our patients. In the literature, many studies evaluated WM changes through a broader perspective by taking tau and amyloid pathology into account. In a follow-up neuroimaging study using MRI [22], increased cerebrospinal fluid (CSF) tau was found to be correlated with increased entorhinal cortex atrophy rate, but MCI patients with lower levels of CSF tau were found to have a higher rate of atrophy if they also had increased WMH load. It was also shown that increased WMHs in parietal lobes predicted progression from

Table 4
Spearman's Rank Correlation Coefficient of ARWMC scores of frontal, parieto-occipital, temporal, basal ganglia and infratentorial regions and volumes of total hippocampus and cerebral white-matter.

	LF	RF	LPO	RPO	LT	RT	LBG	RBG	LINF	RINF
TH	0.028	0.025	0.062	0.134	-0.075	-0.214	-0.092	-0.092	0.153	*
WM	0.092	0.193	-0.036	0.052	-0.050	-0.143	-0.092	-0.092	0.146	*

LF: Left Frontal ARWMC score; RF: Right Frontal ARWMC score; LPO: Left Parieto-Occipital ARWMC score;
RPO: Right Parieto-Occipital ARWMC score; LT: Left Temporal ARWMC score; RT: Right Temporal ARWMC score;
LBG: Left Basal Ganglia ARWMC score; RBG: Right Basal Gaglia ARWMC score; LINF: Left Infratentorial ARWMC score;
RINF: Right Infratentorial ARWMC score; TH: Total Hippocampus volume;WM: Cerebral white matter volume.
* Cannot be computed because at least one of the variables is constant.
**. Correlation is significant at the 0.01 level (2-tailed).

MCI to AD which had the most potent effect in participants with elevated tau levels. In another study using MRI and PET, increased WMHs were significantly associated with frontal hypometabolism in patients who converted from MCI to AD [23]. These results show that, WMHs play a substantial role in the progression of Alzheimer's disease. As a conclusion, WMHs in amnestic MCI patients seem to be related to the cognitive performance of the patients. However, several questions remain to be answered and one of them is how WMHs worsen the deficits of MCI patients. Further longitudinal studies using both biological biomarkers and MRI would help to establish a greater degree of accuracy on this matter.

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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.

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