Evaluation of the Correlation Between Thalamic Area and Cognitive Functions in Patients with Early-Stage Relapsing-Remitting Multiple Sclerosis

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Abstract

Aim: The aim of this study is to investigate the presence of cognitive dysfunction and deep gray matter involvement in the early-stages of Relapsing-Remitting Multiple Sclerosis (RRMS) disease and examine the relationship between them.

Methods: Thirty-four patients and 23 healthy individuals were included in the study. Patients diagnosed with RRMS according to the Revised 2010 and 2017 McDonald criteria, aged between 18-50, were enrolled in the study. The control group consisted of 23 healthy individuals with normal neurological examination, cranial magnetic resonance imaging (MRI), and cognitive functions. All participants underwent a neuropsychological test battery that covers memory, executive functions, language, and visuospatial domains, and the results of these tests were compared among the study groups. The data on MRI parameters, including the areas of the thalamus and corpus callosum as well as the width of the third ventricle, were compared among the study groups. Finally, the relationship between neuropsychological test results and MRI parameters was investigated in patients with early-stage RRMS.

Results: The mean duration of the disease for MS patients was 3.53 years, and their median EDSS score was 2. It was observed that memory, executive functions, and fine motor skills were affected in early-stage RRMS patients. This impairment correlated with a decrease in the thalamus and corpus callosum areas and an increase in the third ventricle width.

Conclusions: The MRI parameters defined as biomarkers for potential cognitive impairments in RRMS have critical importance in predicting the prognosis of the disease and taking early measures against future cognitive dysfunction.

Keywords: *Multiple Sclerosis, deep gray matter, thalamus, cognitive dysfunction*

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system, and is characterized by inflammation, degeneration, axonal loss, and gliosis in both gray and white matter [1]. In MS, the onset age is 20-40 years in 2/3 of patients, and the female-to-male ratio is 2-3/1. Although the exact cause is unknown, autoimmune mechanisms triggered by genetic and environmental factors are thought to play a role in the pathogenesis [2].

Some symptoms which occur due to impairments in motor, sensory, visual, cerebellar, and cognitive functions can be explained by the location, distribution, or burden of plaques in the central nervous system in MS [3]. However, rather than demyelinating plaques, progressive neuronal/axonal loss has recently been identified as a cause of neurological disability [4].

The prevalence of cognitive impairment in MS varies between 40-70%. According to recent studies, the information processing capacity (information processing speed and working memory), episodic memory, verbal fluency, and executive functions are the most affected cognitive parameters in MS, as in subcortical dementia [5–7]. As a result, the form of the disease and the period elapsed until diagnosis play a greater role in predicting the cognitive impairment that the disease may cause in the future, compared to the degree of physical disability caused by the disease or the period elapsed after the diagnosis of the disease [8,9]. Neuropathological processes such as demyelination, neuroaxonal loss, and synaptic loss in cortical and deep gray matter,

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particularly in the thalamus, have recently been shown as causes of cognitive impairment in MS [10–12]. Thalamus plays an important role in cognitive functions such as arousal, executive functions, emotional and episodic memory, spatial learning and memory, and recollective-based and familiarity-based recognition via its connections between the hippocampus, amygdala, cingulate cortex, orbitofrontal cortex, retrosplenial cortex, and inferior parietal lobule [13,14]. One of the most affected parameters among cognitive functions in MS is the process of encoding and recalling information. It is deteriorated as a result of damage of the anterior thalamic region, hippocampus, or any of the remaining other components of the Papez cycle [15]. It has been shown that thalamic atrophy is closely linked to cognitive impairment [16]. Reduced brain volume is also strongly linked to cognitive impairment.

The atrophy that occurs in cortical and subcortical gray matter structures can be observed in the early stages of MS and is an early indicator of cognitive impairment. Therefore, it has significant importance in predicting the prognosis of the disease. The detection of this atrophy through various imaging methods may assist in taking preventive measures against the progression of potential cognitive impairment that may develop from the onset of the disease. Therefore, in this study, we aim to investigate the role of imaging methods in predicting cognitive impairment that may develop in the early stages of MS. We aim to determine the relationship between the degree of cognitive impairment and physical disability in early-stage Relapsing-Remitting Multiple Sclerosis (RRMS) patients and also to determine the correlation between cognitive impairment and the atrophy of the thalamus and cerebral cortex (central atrophy- third ventricle width, corpus callosum area).

2. Materials and methods

2.1. Participants

After the approval of Dumlupınar University, Faculty of Medicine, Clinical Research Ethics Committee (Date: 29.07.2016, No: 2015-KAEK-86/09-178), the study was organized according to the Principles of the Declaration of Helsinki. Between August 2016 and October 2016, patients between the ages of 18 and 50 who were diagnosed with RRMS based on the revised 2010 McDonald criteria and had undergone a cranial magnetic resonance imaging (MRI) within the past three months were included in the study at our clinic. In addition, all patients fulfilled the 2017 McDonald criteria for RRMS. Patients with RRMS who experienced relapse or received steroid therapy in the past three months, as well as those with Primary and Secondary Progressive Multiple Sclerosis (PPMS and SPMS), were excluded from the study. And also, patients with other neurological diseases such as cerebrovascular disease and brain tumors, metabolic disorders (thyroid dysfunction, severe vitamin B12 deficiency, folic acid deficiency), antipsychotics use, alcohol consumption, severe depression (Beck Depression Scale score 21 and above), learning difficulties that may affect cognition, advanced visual defects, and upper extremity motor dysfunction were excluded from the study. Patients were informed about the study, and their written informed consent was provided. Disease severity was evaluated with the Expanded Disability Status Scale (EDSS).

The control group consists of healthy individuals who presented to our outpatient clinic with complaints of headache during the same time period and underwent cranial MRI within the past three months. Having a neurological disease, a major psychiatric disorder, antipsychotics use, chronic alcohol consumption, and a pre-existing learning disability was defined as the exclusion criteria for healthy individuals. Their neurological examination and cranial MRI were normal. Also, their written informed consent was provided. In the Beck Depression Scale, which is administered to all participants and consists of 21 items, each item is scored on a scale of 0 to 3. While the lowest score was 0, the highest score was 63. The range of 0-4 points indicates the absence of depression, while the range of 5-13 points indicates mild depression, the range of 14-20 points indicates moderate depression, and a score of 21 points or higher indicates severe depression [17]. In our study, we excluded participants with severe depression (21 points or higher). In the study, demographic characteristics including age, gender, and education level of the participants were evaluated. A neuropsychological test battery, which included tests assessing attention, memory, language functions, executive functions, visuospatial perception, and structural functions, was administered to all the participants by a neurologist experienced in cognitive tests.

2.2. Neuropsychological evaluation

The Edinburgh Handedness Inventory (EHI) was used to determine the handedness of the participants. The Standardized Mini-Mental State Examination (SMMSE) was applied to the participants for general cognitive assessment. Delphiforfun reaction time test (DRT) was used to evaluate the simple reaction time. Digit Span Test (DST) was used to evaluate verbal attention, and Corsi Block Test (CBT) was used to evaluate visual attention. Both tests assess verbal and visual simple attention, complex attention, short-term memory, and working memory. Oktem verbal memory processes test (OVMPT), Wechsler memory scale visual reproduction (WMS-VR) and logical memory (WMS-LM) subtests were applied to assess short and long-term verbal and nonverbal memory. Each participant's short-term memory score and long-term memory recall+recognition score were determined by the results of these tests. OVMPT is a test used frequently in our country to evaluate verbal memory [18]. The test assesses short-term memory, acquisition of information, keeping the information in the mind, and recalling information by spontaneous or recognition. Pacet Auditory Serial Addition Test (PASAT) was performed to evaluate working memory, calculation ability, and complex attention. Visuospatial perception and construction functions were evaluated with the Benton facial recognition test (BFRT), the judgment of line orientation test (JLOT), and the cube drawing test (CDT). The modified Boston diagnostic aphasia examination (BDAE) and Boston naming test (BNT) were used to evaluate language functions. Clock drawing test, Stroop Color and Word Test (SCWT), Trail Making Test (TMT) Parts A & B, and categorical and lexical verbal fluency (CVFT/LVFT) tests were performed for frontal executive functions. Fine motor skills were evaluated with the nine-hole peg test (NHPT). Abstract thinking and reasoning ability from higher cortical functions were evaluated with verbal comprehension subtests of the Wechsler Adult Intelligence Scale–Revised (WAIS-R), similarities and comprehension. The calculation ability was evaluated with the calculation subtest of the Short Test of Mental Status (STMS). The results of all neuropsychological evaluations were compared between the patient and control groups.

2.3. Magnetic Resonance Imaging

Cranial MRIs of all the participants which were performed between May 2016 and July 2016 in Dumlupınar University Faculty of Medicine, Evliya Celebi Training and Research Hospital, were evaluated.

All cranial MRIs were obtained with a 1.5 T GE Excite (GE Healthcare Technologies, Waukesha, WI, USA) MRI device, and a standard 8-channel head coil was used. Sequence features are as follows; T1-weighted (TR/TE 600/14), T2-weighted (TR/TE 5400/99) and FLAIR images (TR/TE/TI 9000/110/2100) in the axial plane, T2-weighted images in the sagittal-coronal plane. Matrix 256×256, FOV 22 or 24 cm, section thickness 5 mm, cross section spacing 1 mm. Measurements were made manually via the hospital automation system (Siso Viewer - V2.9) by a neuroradiology specialist who is blinded to the clinical status of participants. The width of the third ventricle is the marker that shows the best correlation with the brain parenchymal fraction in cross-sectional studies and is used to evaluate

whole brain atrophy (cerebral atrophy) or central atrophy [19]. In addition, the width of the third ventricle is associated with neocortical volume and is an important marker for cognition [20]. The increase in width of the third ventricle, whose lateral walls are formed by the dorsomedial thalamic nucleus, may represent selective thalamic atrophy. So, it has a strong relationship with many neuropsychological tests. Therefore, we used the width of the third ventricle to evaluate cerebral atrophy in our study. The width of the third ventricle was calculated by measuring the length of a second line drawn perpendicular to the midline of the line drawn parallel to the interhemispheric fissure along the long axis of the third ventricle in the T1-weighted axial section where the third ventricle was best visualized (Figure 1).

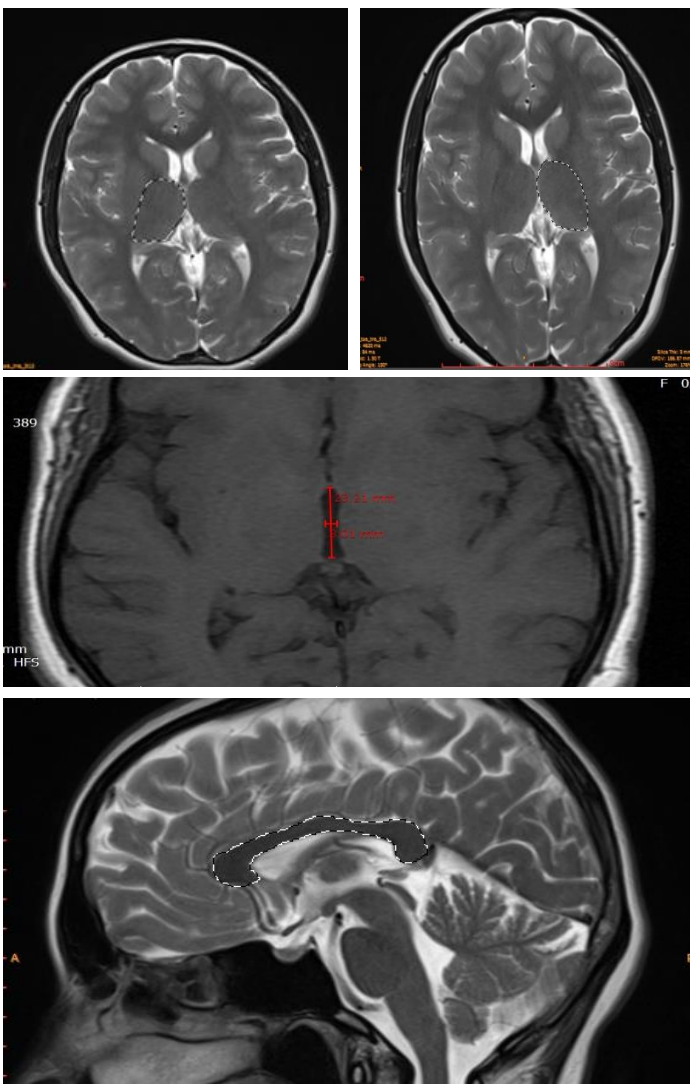

Figure 1
Thalamus Area, Third Ventricular Width and Corpus Callosum Area Measurements

In a study performed by Müller et al. a control group consisting of 70 healthy individuals and a group consisting of 54 patients with RRMS were compared. The upper limit of the normal width of the third ventricle in the control group was determined as 5.06 mm by adding 2 standard deviations (SD) to the mean value, and this value was used as the cut-off value in the study [21]. In a study by Karakaş et al. from Turkey, the normal width of the third ventricle was determined as 3.79±0.85 mm in females and 4.12±0.94 mm in males [22]. According to these results, in our study, the upper limit of the normal value of the width of the third ventricle was defined as 0.5 cm to evaluate cerebral atrophy. The area of the corpus callosum, viewed in the midsagittal plane on T1 or T2 weighted images, was obtained after its circumference was drawn manually. On T2 axial-weighted images, the area of the thalamus was obtained by drawing manually its circumference at the level of the foramen Monro.

2.4. Statistical analysis

All analyses were done with "SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL)". Descriptive statistics were presented as mean±standard deviation, frequency distribution, and percentage. Pearson Chi-Square Test and Fisher's Exact Test were used to evaluate categorical variables. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk Test). According to the results of the normal distributions of the variables, Mann-Whitney U Test was used to compare nonparametric data, and Student's T-Test was used to compare parametric data. The relationship between the variables was evaluated with Spearman Correlation Analysis. Last, in RRMS patients, during the correlation analyses between the results of neuropsychological tests and MRI parameters, the partial correlation analyses were applied to keep under control some demographic data that may affect the neuropsychological tests including age, gender, education period, and Beck Depression Scale scores. Statistical significance level was accepted as $p<0.05$.

3. Results

34 patients and 23 healthy individuals were included in the study. The demographic and descriptive characteristics of the patient and control groups, including age, gender, education period, handedness, and Beck Depression Scale scores, were similar. In addition, the patients' mean disease duration was 3.5 years, and their median EDSS score was 2 (Table 1).

The distribution of neuropsychological evaluation results between the study groups is presented in Table 2. The long-term memory scores of OVMPT, WMS-VR, and WMS-LM, as well as the short-term memory score of WMS-LM, were found lower in patients with RRMS.

Table 1
Distribution of some demographic and descriptive characteristics between study groups

	RRMS patients (n=34)	Control group (n=23)	p
Age (years), $\bar{X}$±S	35,32±8,04	32,57±7,45	0,196a
Gender, n (%)			
Female	27 (79,4)	17 (73,9)	0,627b
Male	7 (20,6)	6 (26,1)	
Education period, n (%)			
≤8 years	19 (55,9)	8 (34,8)	0,118b
>8 years	15 (44,1)	15 (65,2)	
Duration of disease (years), $\bar{X}$±S	3,53 (3,48)	----------	-------
Severity of disease (EDSS), M(IQR)	2 (0,5-2)	----------	-------
Beck Depression Scale score, $\bar{X}$±S	6,94 (5,03)	7,61 (6,33)	0,800c
The handedness (EHI)			
Right	33 (97,1)	21 (91,3)	0,559d
Left	1 (2,9)	2 (8,7)	

Table 2
Distribution of neuropsychological evaluation results between study groups

	RRMS patients (n=34) $\bar{X}$±S	Control group (n=23) $\bar{X}$±S	P
General Cognitive Assessment			
SMMSE	27,38±1,79	28,30±1,55	0,032[b]
Reaction Time			
DRT-Auditory Modality(s)	0,43±0,10	0,40±0,11	0,084[b]
DRT- Visual Modality(s)	0,36±0,08	0,34±0,04	0,714[b]
Attention			
Digit Span Test	9,15±1,91	9,61±2,10	0,399[b]
Forward-Backward Difference ≤2, n (%)	31 (91,2)	22 (95,7)	0,641[c]
Forward-Backward Difference>2, n (%)	3 (8,8)	1 (4,3)	
Corsi Block Test	11,12±1,59	11,09±1,24	0,938[a]
Forward-Backward Difference ≤2, n (%)	32 (94,1)	23 (100)	0,510[c]
Forward-Backward Difference>2, n (%)	2 (5,9)	0	
Memory			
OVMPT- Short Term Memory	111,91±20,30	120,13±14,18	0,157[b]
OVMPT- Long Term Memory/Recall	12,0±2,93	12,78±1,91	0,497[b]
OVMPT- Long Term Memory/Recognition	2,50±2,26	2,22±1,91	0,811[b]
OVMPT- Long Term Memory/Total Score	14,50±1,46	15,00±0	0,013[b]
WMS-VR- Short Term Memory	9,27±3,36	10,09±2,73	0,342[b]
WMS-VR- Long Term Memory/Recall	7,27±3,70	8,91±3,19	0,087[a]
WMS-VR- Long Term Memory/Recognition	2,88±2,76	4,00±3,38	0,205[b]
WMS-VR- Long Term Memory/Total Score	10,15±4,02	12,91±1,99	0,005[b]
WMS-LM- Short Term Memory	6,27±3,06	8,00±2,52	0,028[a]
WMS-LM- Long Term Memory/Total Score	4,71±3,34	6,39±2,41	0,042[a]
Working Memory			
PASAT	33,21±12,61	42,87±11,45	0,005[a]
Visuospatial perception and construction			
Benton Facial Recognition Test	41,18±4,35	42,52±3,46	0,233[b]
Judgment of Line OrientationTest	19,21±5,88	21,65±4,88	0,105[a]
Cube Drawing Test	4,44±0,79	4,57±0,73	0,538[b]
Language Functions			
Boston Naming Test	28,97±1,43	29,48±0,90	0,142[b]
Frontal Executive Functions			
Clock Drawing Test	3,79±0,54	4,00±0	0,057[b]
Stroop Color and Word Test-1 (s)	9,74±3,43	8,43±0,99	0,143[b]
Stroop Color and Word Test-2 (s)	12,27±3,32	10,39±1,92	0,010[b]
Stroop Color and Word Test-3 (s)	16,85±4,69	14,17±3,61	0,014[b]
Stroop Color and Word Test-4 (s)	24,21±7,47	24,13±6,94	0,896[b]
Trail Making Test-A (s)	41,06±21,82	30,43±13,21	0,028[b]
Trail Making Test-B (s)	103,85±54,42	76,04±31,95	0,018[b]
Categorical Verbal Fluency	21,06±4,74	22,35±5,91	0,366[a]
Lexical Verbal Fluency	12,53±5,52	13,13±5,14	0,680[a]
Fine Motor Skills			
Nine Hole Peg Test-Dominant Hand (s)	16,97±2,74	15,52±1,44	0,029[b]
Nine Hole Peg Test-Nondominant Hand (s)	18,97±2,52	16,57±0,99	<0,000[b]
Higher Cortical Functions			
WAIS-Verbal Comprehension/Similarities	15,56±4,27	16,00±3,84	0,833[b]
WAİS-Verbal Comprehension/Comprehension	14,41±3,47	14,87±3,88	0,643[a]
STMS- Calculation	5,82±2,05	6,43±2,08	0,202[b]

$\bar{X}$: Mean; S: Standard Deviation, SMMSE: Standardized Mini-Mental State Examination; DRT: Delphiforfun Reaction Time Test; OVMPT: OktemVerbal Memory Processes Test; WMS-VR: Wechsler Memory Scale-Visual Reproduction; WMS-LM: Wechsler Memory Scale-Logical Memory; PASAT: Pacet Auditory Serial Addition Test; WAIS: Wechsler Adult Intelligenc eScale; STMS: Short Test of Mental Status, aStudent's T Test, bMann-Whitney U Test; cFisher'sExact Test

Table 3
Distribution of results of MRI measurement between study groups

	RRMS patients (n=34)	Control group (n=23)	P
MRI measurements			
Left thalamus area (cm2), $\bar{X}$±S	5,19±0,76	6,02±0,73	<0,000a
Right thalamus area (cm2), $\bar{X}$±S	5,23±0,76	6,08±0,68	<0,000a
Corpus Callosum area (cm2), $\bar{X}$±S	5,51±1,01	6,06±0,70	0,017a
The width of third ventricle (cm), $\bar{X}$±S	0,43±0,23	0,27±0,14	0,005b
Cerebral atrophy (>0,5 cm), n (%)	11 (32,4)	1 (4,3)	0,018c

$\bar{X}$: Mean; S: Standard Deviation, aStudent's T Test;bMann-Whitney U Test; cFisher's Exact Test

Table 4
The relationship between the demographic characteristics of the control group and their MRI parameters

Control group (n=23)	Age (years)	Gender (female / male)	Education period (≤8 years / >8 years)	Beck depression scale score
	r	r	r	r
MRI measurements				
Left thalamus area (cm^2)	-0,059	0,194	-0,096	-0,031
Right talamus area(cm^2)	-0,155	0,224	-0,041	-0,157
Corpus Callosum area (cm^2)	-0,058	-0,179	-0,385	-0,148
The width of third ventricle (cm)	0,213	0,479*	0,200	0,046

*p<0,05; r: Spearman Correlation Coefficient. MRI: Magnetic Resonance Imaging

Table 5
The relationship between the demographic characteristics of the RRMS patients and their MRI parameters

RRMS patients (n=34)	Age (years)	Gender (female / male)	Education period (≤8 years / >8 years)	Beck depression scale score	Duration of disease (years)	Severity of disease (EDSS score)
	r	r	r	r	r	r
MRI measurements						
Left thalamus area (cm^2)	-0,274	0,185	0,229	-0,130	-0,322	-0,308
Right talamus area(cm^2)	-0,301	0,211	0,236	-0,096	-0,296	-0,288
Corpus Callosum area (cm^2)	0,048	0,063	-0,190	-0,070	-0,241	-0,273
The width of third ventricle (cm)	0,283	0,126	-0,151	0,126	0,429*	0,226

*p<0,05; r: Spearman Correlation Coefficient, MRI: Magnetic Resonance Imaging

In addition, the scores of SMME and PASAT were detected lower in the patients. The completion durations of tests including SCWT-2/3, TMT-A/B, and NHPT-Dominant/Nondominant hand were longer in the patients (p<0.05, Table 2). Other neuropsychological test results were statistically similar between groups.

In the patients, the areas of the right thalamus, left thalamus, and corpus callosum were lower, while the width of the third ventricle was higher (p<0.05, Table 3). In proportion to the increase in the width of the third ventricle, the percentage of RRMS patients with cerebral atrophy was significantly higher than in the control group (32.4% vs. 4.3%, p=0.019, Table 3).

In healthy individuals, the width of the third ventricle tended to be higher in the male population (r=0.479, p<0.05, Table 4).

However, in the patients, when the relationship between MRI parameters and demographic data was evaluated, only the width of the third ventricle showed a significant moderate positive correlation with disease duration (r=0.429, p<0.05, Table 5).

In the patients, the relationship between neuropsychological test results and MRI parameters was investigated through partial correlation analysis, controlling for demographic variables such as age, gender, education period, and Beck Depression Scale score that could affect the neuropsychological test results (Table 6).

In the patients with RRMS, based on the neuropsychological tests that were shown to be affected compared with the tests results of the healthy individuals (Table 2), a moderate positive correlation between OVMPT- Long-term memory total score and the areas of right and left thalamus (r=0.471, r=0.414, respectively), as well as a moderate positive correlation between PASAT score and right thalamus area was detected (r=0.395). In addition, while the completion durations of SCWT-2 and TMT-A showed a moderate positive correlation with the width of the third ventricle (r=0.372, r=0.423, respectively), TMT-B completion duration showed a negative, moderate correlation with the areas of the right and left thalamus (r=-0.538, r=-0.500, respectively). Finally, it was detected that there was a negative, moderate correlation between the completion duration of the NHPT-Dominant hand and the areas of the right thalamus, left thalamus, and corpus callosum (r=-0.476, r=-0.466, r=-0.631, respectively) and a negative, moderate correlation between the completion duration of the NHPT-Nondominant hand and the areas of the right thalamus and corpus callosum (r=-0.441, r=-0.534, respectively).

In addition, a correlation was found between the results of tests such as the OVMPT-Short-Term Memory and WAIS-Verbal Comprehension/Comprehension, which are similar among working groups, and thalamic areas. While there is a moderate positive correlation between OVMPT-Short-Term Memory scores and the right and left thalamic areas (r=0.390, r=0.397, respectively), a moderate positive correlation was detected between WAIS-Verbal Comprehension/Comprehension test scores and the right thalamic area (r=0.394).

4. Discussion

Cognitive dysfunction is observed in 35-60% of MS patients, and although this impairment is strongly correlated with disease progression, it is weakly correlated with disease duration and physical disability caused by the disease [23,24]. Studies have shown that 80% of patients with Clinical Isolated Syndrome (CIS) have deterioration in at least one cognitive area, and 57% have deterioration in two or more cognitive areas. These rates are similar to those of newly diagnosed (2-3 years) RRMS patients [25,26]. Recent studies have shown that cognitive impairment is seen in all forms of MS and is more pronounced and more common in progressive forms of MS. Consistent with this, it was found to be 20-25% in Radiological Isolated Syndrome (RIS), 30-45% in RRMS, and 50-75% in SPMS [27]. In a study by Amato et al., 45 MS patients with a mean disease duration of 1.5 years were followed for 10 years. While 74% of the cases were cognitively normal at baseline, this rate decreased to 51% at 4 years and to 44% at 10 years [28]. Recently, advanced imaging modalities have revealed that cognitive impairment in MS is closely related to cortical T2 demyelinating lesion volume and T1 hypointense lesion burden on MRI, and has a strong negative correlation with the brain parenchym-

Table 6

The relationship between MRI measurements and neuropsychological evaluation results of RRMS patients

RRMS patients (n=34)	Left thalamus area(cm^2) r	Right thalamus area(cm^2) r	Corpus Callosum area(cm^2) r	The width of third ventricle(cm) r
SMMSE	0,180	0,232	0,162	-0,161
DRT-Auditory Modality (s)	0,213	0,128	-0,010	-0,069
DRT- Visual Modality (s)	0,234	0,248	0,006	0,159
Digit Span Test	-0,119	-0,032	0,110	-0,033
Corsi Block Test	-0,201	-0,220	0,204	-0,320
OVMPT- Short Term Memory	*0,397**	*0,390**	0,038	-0,289
OVMPT- Long Term Memory/Recall	0,301	0,324	0,239	-0,272
OVMPT- Long Term Memory/Recognition	-0,122	-0,115	-0,184	0,171
OVMPT- Long Term Memory/Total Score	*0,414**	*0,471***	0,194	-0,281
WMS-VR- Short Term Memory	0,197	0,300	0,312	-0,286
WMS-VR- Long Term Memory/Recall	0,120	0,276	0,143	-0,223
WMS-VR- Long Term Memory/Recognition	0,223	0,104	0,316	-0,096
WMS-VR- Long Term Memory/Total Score	0,268	0,293	0,359	-0,246
WMS-LM- Short Term Memory	-0,064	-0,067	-0,029	0,076
WMS-LM- Long Term Memory/Total Score	0,059	0,038	0,052	0,064
PASAT	0,310	*0,395**	0,273	-0,065
Benton Facial Recognition Test	0,009	0,067	0,130	-0,156
Judgment of Line Orientation Test	-0,055	0,096	0,179	-0,141
Cube Drawing Test	-0,274	-0,167	-0,077	-0,100
Boston Naming Test	-0,136	-0,073	-0,043	-0,055
Clock Drawing Test	0,084	0,196	-0,093	0,246
Stroop Color and Word Test-1 (s)	0,181	0,163	-0,155	0,343
Stroop Color and Word Test-2 (s)	0,003	-0,049	-0,105	*0,372**
Stroop Color and Word Test-3 (s)	-0,064	-0,131	-0,217	0,225
Stroop Color and Word Test-4 (s)	0,057	0,044	0,071	-0,026
Trail Making Test-A (s)	-0,227	-0,277	-0,163	*0,423**
Trail Making Test-B (s)	*-0,500***	*-0,538***	-0,132	0,344
Categorical Verbal Fluency	0,083	0,091	0,076	0,025
Lexical Verbal Fluency	0,013	0,152	-0,184	0,057
Nine Hole Peg Test-Dominant Hand (s)	*-0,466***	*-0,476***	*-0,631***	0,243
Nine Hole Peg Test-Nondominant Hand (s)	-0,349	*-0,441**	*-0,534***	0,260
WAIS-Verbal Comprehension/Similarities	0,288	0,323	0,051	-0,037
WAiS-Verbal Comprehension/Comprehension	0,329	*0,394**	0,159	0,020
STMS- Calculation	0,292	0,289	0,310	0,096

*p<0,05; **p<0,01; r: Spearman Correlation Coefficient, During the Spearman Correlation analyses, demographic data that may affect the neuropsychological test results including age, gender, education duration, and Beck depression inventory results were kept under control with partial correlation analysis. SMMSE: Standardized Mini-Mental State Examination; DRT: Delphiforfun Reaction Time Test; OVMPT: Oktem Verbal Memory Processes Test; WMS-VR: Wechsler Memory Scale-Visual Reproduction; WMS-LM: Wechsler Memory Scale-Logical Memory; PASAT: Pacet Auditory Serial Addition Test; WAIS: Wechsler Adult Intelligence Scale; STMS: Short Test of Mental Status

-al fraction showing cortical atrophy [29]. It has been reported that cognitive impairment due to these pathologies is particularly evident in the areas of memory, processing speed and verbal fluency [29]. Furthermore, similar pathologies such as inflammation, demyelination, and neuronal loss in deep gray matter, particularly in the thalamus, have been linked to cognitive impairment in MS patients. For this purpose, we planned to investigate the relationship between cognitive impairment, which may be seen in early-stage RRMS patients, and thalamic and cortical cerebral atrophy. In this context, the fact that the patients in our study had a mean disease duration of 3.5 years and a median EDSS score of 2 indicates that the majority of the patients in our study were in the early-stages of RRMS. However, it has been shown in previous studies that EDSS is insufficient for assessing cognitive ability [30].

It has been reported previously that education period is one of the best indicators of cognitive reserve, which refers to the ability of the brain to tolerate underlying pathological processes associated with disease without manifesting symptoms or signs [31]. In a longitudinal study that determined the cutoff value of the education period for the cognitive reserve to be 9 years, a significant decline was observed in cognitive tests performed at regular intervals in MS patients with low cognitive reserve, while no significant changes were detected in MS patients with high cognitive reserve [32]. Based on this information, we determined the threshold value of education period, an indicator of cognitive reserve, to be 8 years, as compulsory education in our country lasts for 8 years. Therefore, individuals with an education period of 8 years or less are thought to have lower cognitive reserves. Similar demographic characteristics, including education period, among the study groups, have enabled a more objective evaluation of the neuropsychological test results in our study.

MS can affect all areas of cognition, and cognitive decline in MS typically manifests in the domains of episodic memory, information processing efficiency (processing speed and working memory), and executive functions [5].

In the PASAT, which is used to evaluate working memory, one of the most important functions of the dorsolateral prefrontal cortex with strong connections to the thalamic nuclei, deterioration was detected in approximately 20-25% of patients with CIS and early-stage RRMS [26]. In the studies conducted by Forn et al. [33] in 30 MS patients, Locatelli et al. [34] in 39 RRMS patients, and Deloire et al. [35] in 44 early-stage RRMS patients, significant deterioration was found in the PASAT and symbol digit modalities test (SDMT), which evaluate information processing speed and working memory, as well as in the

SCWT test, which evaluates attention and interference. Achiron et al. reported an average 10% decrease in PASAT 2 scores in MS patients 5 years after disease onset [36]. In this context, thalamic volume is associated with many tests that evaluate working memory such as PASAT and SDMT [37]. Barak et al. administered the clock drawing test, which is used to evaluate working memory as well as visuospatial construction, to 107 RRMS patients. The sensitivity of this test was found to be 93.4% and the specificity was 85.8%, and it was observed that most RRMS patients scored low on this test [38]. The SCWT, which primarily evaluates focused attention, information processing speed, and inhibition of inappropriate responses, among frontal executive functions, was applied to 25 MS patients by Macniven et al., [39] and a significant impairment was observed in this test in MS patients compared to healthy controls. In another study, an abnormality in SCWT was found in approximately 35% of early-stage MS patients [40]. In line with these findings, our study revealed an impairment in the frontal executive functions in early-stage RRMS patients compared to healthy individuals, as evidenced by the low scores on PASAT and prolonged durations of SCWT-2/3, TMT-A/B.

Long-term memory is one of the most affected parameters in the MS, like working memory. Accordingly, Duque et al. evaluated a group of 44 patients with all types of MS every 3 months for 2 years. Cognitive impairment, which was 31% at baseline, increased to 41% at the end of the 2nd year. It was determined that this impairment was most pronounced in verbal memory and information processing speed [41]. Janculjak et al stated that the impairment in long-term memory function in MS patients is in the stages of storing and recalling of information [42]. Besides the impairment in visual and verbal long-term memory, Litvan et al. also found a deterioration in short-term memory functions in MS patients [43]. In this context, the low long-term memory scores of OVMPT, WMS-VR, and WMS-LM, as well as the low short-term memory score of WMS-LM, identified in our study, provide evidence for the impairment of memory functions, especially long-term memory functions, in early-stage RRMS patients.

The main responsible regions for the praxis are the frontal and parietal cortical areas as well as the basal ganglia. Finally, in a study by Longstaff et al. evaluating fine motor skills, it was observed that patients with MS drew the spiral on the graphic tablet slower, applied less pressure to the pen, and deviated more from the ideal drawing on the spiral test [44]. In our study, fine motor skills of early-stage RRMS were evaluated with NHPT. In accordance with the literature, we detected that the completion duration of NHPT-Dominant/Nondominant hand was longer in patients with RRMS.

Thalamic axons carry information between subcortical and cortical areas. Damage to the thalamic nuclei and their connections causes a variety of symptoms, including cognitive impairment [14]. Although it has been observed that thalamic volume loss correlated with reduced brain parenchymal fraction in MS, thalamic atrophy is more prominent and selective in MS [45]. Demyelinating plaques causing secondary axonal damage in deep gray matter, the thalamic hypometabolism which occurs due to cerebral demyelinated plaques and axon loss, iron deposition in the thalamus leading to lipid peroxidation and oxidative stress have been reported among the reasons for this selective involvement of the thalamus [45]. Also, the decrease in these thalamic areas in MS patients can be attributed to neuronal loss secondary to diffuse macrophage/microglial activation, CD8 T lymphocyte-mediated cytotoxicity occurring in normal-appearing gray matter [46,47]. Furthermore, the relationship between thalamic hypometabolism and cognitive decline has been reported in a PET study [48]. The studies have revealed that volume loss in the thalamus is one of the earliest and most significant findings of subcortical gray matter pathology in CIS cases, and progressive atrophy of the thalamus is also observed in all other types of MS [49]. In an autopsy study involving 14 RRMS and SPMS patients, Vercellino et al. demonstrated that lesions affecting both the gray and white matter of the thalamus are predominantly located in the anterior and dorsomedial nuclei, which are associated with cognitive functions and form the periventricular surface of the thalamus [46]. Cifelli et al. reported a decrease in the volume of the total and dorsomedial nuclei of the thalamus due to decreased neuronal density distant from focal demyelinating lesions [50]. Despite studies reporting no correlation between cognitive deficits and thalamic volume loss, in line with several other studies, our study found a relationship between thalamic area, the width of the third ventricle with cognitive performance in MS patients. In our study, it was found that the areas of the right thalamus, left thalamus, and corpus callosum were lower, while the width of the third ventricle was higher in RRMS patients. Also, the cases with cerebral atrophy which was determined according to the width of the third ventricle were higher in the RRMS group (32.4% vs. 4.3%, p=0.019). In early-stage RRMS patients, this increase in the width of the third ventricle can be attributed to atrophy of the thalamus, especially the dorsomedial nucleus, which has tight connections with the prefrontal cortex, or specifically to a reduction in neocortical volume, particularly since this width is the linear marker that best correlates with the brain parenchymal fraction [51].

The decrease in thalamic volume in patients with MS is associated with a decline in scores of cognitive tests assessing information processing speed, verbal fluency, working memory, verbal and visuospatial memory, and executive functions [37,45]. A study that compared healthy controls to MS patients found that the increase in the width of the third ventricle was a strong predictor of impairment in information processing speed and memory tests [20]. Another study conducted by Papathanasiou et al. showed that cognitive functions such as long-term memory, reaction time, and executive functions assessed by the TMT A/B and lexical fluency, as well as all MRI parameters including third ventricle width, corpus callosum area, and thalamic area, were affected in patients with RRMS compared to healthy individuals. In this study, a strong positive correlation was observed between all atrophy measurements (corpus callosum area, thalamic area, and third ventricle width) and all cognitive indicators, and a mild to moderate correlation was found between total lesion volume and cognitive tests [52]. Tiemann et al. reported that parenchymal atrophy was the determinant of possible future cognitive impairment, and this atrophy showed a strong negative correlation with the width of the third ventricle, but did not correlate with lesion load [53]. Rimkus et al. have demonstrated that the lesion load of the corpus callosum and the whole brain were similar in diffusion tensor imaging examinations in MS patients with normal cognition and those with cognitive impairment, but the axonal loss in the corpus callosum was higher in patients with cognitive dysfunction. Additionally, this study reported significant impairments in attention, information processing speed, executive functions, and memory functions in MS patients with more microscopic corpus callosum lesions [54].

Our study investigated the influence of demographic data on all MRI parameters examined in both healthy individuals and RRMS patients. With the exception of a tendency towards greater third ventricle width in male populations in healthy individuals and a significant moderate positive correlation between third ventricle width and disease duration in RRMS patients, no demographic data was found to have an effect on MRI parameters. Furthermore, partial correlation analysis controlling for demographic data such as age, gender, education period, Beck Depression scale scores, and EDSS scores that could affect neuropsychological tests allowed for a more specific

examination of the relationship between MRI parameters and neuropsychological tests in RRMS patients.

In our study, in line with the literature, a moderate positive correlation was found between thalamic areas and executive functions evaluated with PASAT and TMT-B, and also between thalamic areas and long-term verbal memory evaluated with OVMPT. We found a negative, moderate correlation between the width of the third ventricle and executive functions evaluated with SCWT-2 and TMT-A. Additionally, our study demonstrated a moderate, positive correlation between fine motor skills evaluated by NHPT and the areas of the thalamus and corpus callosum. Also, as the duration of the disease increases, the deterioration in MRI parameters related to cognitive functions such as the increase in third ventricle width is consistent with the literature, and this condition suggests that cognitive functions worsen as disease duration increases in patients with RRMS. However, the lack of a significant correlation between EDSS and any of these MRI parameters suggests that EDSS may be inadequate in evaluating cognitive functions.

Finally, in our study, the correlation between thalamic areas and short-term memory evaluated by OVMPT and abstract conceptualization evaluated by WAIS-Verbal Comprehension test in early-stage RRMS patients has suggested that short-term memory and abstract conceptualization may deteriorate in the advanced stages of RRMS, because of the scores of these tests were similar among the study groups.

The relationship between thalamic atrophy and long-term memory, working memory, and executive functions in our study suggests that pathological processes associated with MS affect reciprocal innervation between the thalamic nuclei, particularly the dorsomedial and anterior nuclei, and the dorsolateral prefrontal cortex, orbitofrontal cortex, and limbic system. Our study demonstrates that thalamic atrophy is the best predictor of impaired memory, psychomotor speed, and executive functions in MS patients, and in line with the literature, it has shown a strong correlation with the width of the third ventricle [55].

Among the limitations of the study, it can be noted that the population of sample group is small size, and due to technical reasons, the volumes of the thalamus and corpus callosum cannot be measured. Additionally, although all MRIs were assessed by a neuroradiologist who was blinded to the individuals in the study groups, the manual execution of the area measurements due to technical reasons can also be considered as another limitation of the study.

5. Conclusions

Our study found that many cognitive domains, especially executive and memory functions, are affected even in the early stages of RRMS patients. Moreover, this study revealed that the cognitive deficits observed in early-stage RRMS patients are associated with subcortical gray matter changes, particularly thalamic atrophy, and the width of the third ventricle, which serves as an indicator of both cortical and thalamic atrophy. These MRI parameters, which are indicative of cognitive deficits that may develop in the future, are of great importance in predicting the prognosis of the disease and taking early precautions against potential cognitive dysfunction that may develop in the future.

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Statement of ethics

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Dumlupınar University, Faculty of Medicine, Clinical Research Ethics Committee (Date: 29.07.2016, No: 2015-KAEK-86/09-178).

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

Abbreviations

BDAE: Boston Diagnostic Aphasia Examination
BFRT: Benton Facial Recognition Test
BNT: Boston Naming Test
CBT: Corsi Block Test
CIS: Clinical Isolated Syndrome
CVFT: Categorical Verbal Fluency Test
DRT: Delphiforfun Reaction Time Test
DST: Digit Span Test
EDSS: Expanded Disability Status Scale
EHI: Edinburgh Handedness Inventory
JLOT: Judgment of Line Orientation Test
LVFT: Lexical Verbal Fluency Test
MRI: Magnetic Resonance Imaging
MS: Multiple Sclerosis
NHPT: Nine Hole Peg Test
OVMPT: Oktem Verbal Memory Processes Test
PASAT: Pacet Auditory Serial Addition Test
PPMS: Primary Progressive Multiple Sclerosis
RRMS: Relapsing-Remitting Multiple Sclerosis
SCWT: Stroop Color and Word Test
SMMSE: Standardized Mini-Mental State Examination
SPMS: Secondary Progressive Multiple Sclerosis
STMS: Short Test of Mental Status
TMT: Trail Making Test
WAIS-R: Wechsler Adult Intelligence Scale – Revised
WMS-VR: Wechsler Memory Scale-Visual Reproduction
WMS-LM: Wechsler Memory Scale-Logical Memory

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