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ANALOGICAL REASONING IN MULTIPLE SCLEROSIS

MULTİPL SKLEROZDA ANALOJİK AKIL YÜRÜTME

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Öz

Amaç
Multipl sklerozda yaygın olan bilişsel bozukluk hastalığın tüm evrelerinde gelişebilir ve günlük yaşam aktivitelerini, mesleki, sosyal ilişkileri ve yaşam kalitesini önemli ölçüde olumsuz etkiler. İki durum arasındaki ortak ilişkiyi tanımlama ve bu ortak benzerlikler üzerinden yeni çıkarımlar üretebilme becerisi olan analojik akıl yürütme, insanların günlük yaşamda çok çeşitli problem çözme bağlamlarında ve karar vermede rutin olarak kullandıkları, insan bilişinin temel ögelerinden birisidir. Çalışmanın amacı MS'li bireylerde analojik akıl yürütme becerilerini değerlendirmektir.

Gereç ve Yöntem
Bu gözlemsel, olgu-kontrol çalışması herhangi bir bilişsel yakınması olmayan 30 MS hastası ve yaş, cinsiyet ve eğitim açısından eşleştirilmiş 30 sağlıklı kişiyi kapsamaktadır. Tüm katılımcılara çalışma belleği, dikkat, yürütücü işlevler ve kavram oluşturma ve analojik akıl yürütmeye vurgu yapılan kapsamlı bir nöropsikolojik değerlendirme yapılmıştır.

Bulgular
MS'li hastaların çalışma belleği, dikkat ve yürütücü işlevlerdeki performansları daha kötüydü. Genel olarak MS hastaları ve sağlıklı kontroller arasında kavram oluşturma, soyutlama, bilişsel esneklik ve analojik akıl yürütme açısından bir fark gözlenmedi. Bununla birlikte, bu ödevlerde ilerleyen yaşla birlikte ve hastalık süresi ile orta derecede bir bağıntı gösteren daha kötü bir performans izlenmiştir.

Sonuç
Herhangi bir bilişsel yakınması olmayan, görece genç ve özürlülüğü düşük MS hastalarında bile bilişsel işlev bozukluğu saptanabilmektedir. Erken dönemdeki kognitif rezervler analojik akıl yürütme görevlerinde sağlıklı kontrollere benzer bir performans için yeterli olsa da ilerleyen yaşla birlikte önemli bir bozulma gösterirler. Analojik akıl yürütme görevlerinde sağlıklı kontrollere benzer bir performans için yeterli olsa da ilerleyen yaşla birlikte önemli bir bozulma gösterirler.

Anahtar Kelimeler: Analojik akıl yürütme, Bilişsel işlevler, Multipl skleroz

Abstract

Objective
Cognitive impairment is common in multiple sclerosis (MS) and occurs at all stages of the disease with a significant negative effect on daily life activities, vocation, social relationships and quality of life. Analogical reasoning involves identifying a common relational system between two situations and then generating further inferences driven by these shared commonalities that is a fundamental aspect of human cognition people routinely use in everyday life, in a wide range of problem-solving contexts and decision making. The aim of the study is to evaluate analogical reasoning skills in individuals with MS.

Material and Method
This observational case-control study covers 30 MS patients without any cognitive complaint and

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30 age-, sex- and education-matched healthy person. All participants were underwent a thorough neuropsychological evaluation with emphasis on working memory, attention, executive functions and concept formation and analogical reasoning.

Results
MS patients' performance on working memory, attention and executive functions were worse in comparison to the control group. In general no difference was observed regarding concept formation, abstraction, cognitive flexibility and analogical reasoning between MS patients and healthy controls. However MS patients with advanced age exhibited a poor performance in these tasks which also showed a moderate correlation with disease duration.

Conclusion
Cognitive dysfunction can be detected even in MS patients who are relatively young and have low disability, without any cognitive complaints. Although early cognitive reserves are sufficient for performance in analogical reasoning tasks similar to that of healthy controls, they show significant deterioration with advancing age.

Keywords: Analogical reasoning, Cognitive functions, Multiple sclerosis

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system. In addition to visual, motor and sensory signs and symptoms, cognitive decline is one of the main features of multiple sclerosis in all disease stages and types. Cognitive decline is regarded one of the core features of the multiple sclerosis covering all disease stages and clinical course types. Estimated prevalence of cognitive problems ranges from 34 to 65 % (1-4). Cognitive impairment was suggested as the most probable important determinant of the life quality at all stages of the disease; affecting patients' physical independence, competence in daily activities, employment, coping strategies, symptom management, medication adherence and rehabilitation potential (5).

There is a wide variety of cognitive problems in MS patients. Even so, the most commonly noted domains to be involved are memory, attention, information processing speed, and executive functions (5,6). Besides physical disability, altered decision-making capacity and emotional reactivity observed in MS patients may contribute to the impairment seen in daily functioning (7). Not only physical burden but also cognitive impairments makes MS patients to encounter many challenges in carrying out everyday activities demanding the planning ability, information manipulation, initiation and termination of activities and recognition of errors. One of the constant challenges in execution of these tasks to cope with real-world situation problems is analogical reasoning. Analogical reasoning, which is an integral part of inductive reasoning and problem solving people face in real world situations, plays an omnipresent function in a person's daily life. Analogical reasoning requires processing and transfer of information or meaning acquired in one situation or context to another to identify systematic relational correspondences (8-10). Analogies are important for understanding and interpreting (deciphering) novel incoming information based on past experiences (9, 11). Drawing successful analogies demands grasping the relations among elements in a given situation and offers one to identify distinctive situations, derive veiled causes of observed events, introduce general rules to new situations and deduce new abstractions from experience. Analogical reasoning is also thought to play an important function in learning and problem solving (12). Analogical reasoning has a tight relation with the executive functions, including working memory content, inhibitor control and the faculty of shifting attention to related attributes and passing over the irrelevant ones.

MS is a long-standing disease and the chronic nature of the disease influences treatment adherence and compliance negatively. Evaluations showed that approximately 17 to 36% of patients receiving injectable immunomodulatory treatments nonadhere to therapy, with ratios comparable to other chronic diseases (13). Forgetting the medication, injection anxiety, perceived lack of efficacy, adverse effects of drugs, complacency issues, and treatment fatigue are reported as barriers to maintaining treatment adherence in MS patients (14, 15). Besides given factors, cognitive problems may also affect treatment adherence. It can be speculated that a defective analogical reasoning might cause patients to make up inappropriate decisions about themselves.

In this research, we aimed to evaluate if the reasoning ability affected in MS patients. For this purpose we used the Raven's Standard Progressive Matrices

test and a modified 10-item version of the Visual-Verbal Test. Raven's standard progressive matrices test evaluates abstract reasoning ability and Visual-verbal test (VVT) assess concept formation, abstraction and cognitive flexibility.

Material and Method

For this observational, case-control study 30 patients with a definite relapsing-remitting MS (RRMS) diagnosis who have no cognitive complaint was enrolled (16). The age of patients ranged from 18 to 49 years, and they had 5 to 17 years of education. A control group of healthy individuals were selected among patients' relatives and friends (matched with MS patients for age, gender and education level) who accepted to take part in the study. All MS patients underwent standard medical evaluations, neuro-imaging and cerebral spinal fluid analysis. In order to minimize the possible inferences patients with visual functional scale >1, motor functional scale >2 and expanded disability status scale (EDSS) >3; with an attack in the last 3 months; and having co-existent clinical conditions (depression, thyroid dysfunction, hypertension, diabetes, infection, any other disease) that may interfere cognitive functions were excluded.

The study was approved by university's local research ethics committee (Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee, 07.03.2012/1064) was conducted in line with the principles of the Helsinki Declaration and all the evaluations were done after subjects signed the written consent statement form. RRMS patients and controls were subjected to a detailed neuropsychological evaluation. Neuropsychological evaluations were performed in a single session by one of the investigators individually and the tests were performed in the same order to both groups. All participants were underwent Mini-Mental State Examination (MMSE) (17, 18). Working memory, attention and executive functions were evaluated with the Trail Making Test part A and B, digit span test forward and backward, and Paced Auditory Serial Addition Task (PASAT) (19, 20). The Beck Depression Inventory (BDI) was used to assess mood (21, 22). For concept formation and analogical reasoning Raven's progressive matrices test and visual-verbal test has been used.

Raven's Progressive Matrices Test

Raven's (RPMT) is a paper and pencil test composed of a series of visual pattern matching and analogy problems depicted in abstract figures (23, 24). The RPMT contains five sections, each with 12 items. In each item subjects are given an incomplete design and eight alternatives among which the best one completing the design must be chosen. For each correct answer 1 point is given. Either sum-scores of each section or total score may be used. The items increase in difficulty, and so do the each section of the test. RPMT is composed of abstract pattern match problems and deciphering the correct answers does not depend on previously memorized or semantic knowledge, but rather on the active perceptual and representational analyses of the given item series. The subjects are expected to learn from items, since information and strategies acquired by solving previous items is necessary in order to solve the subsequent ones (24). Test demands neither language nor academic skills for success but education influences performance to a small degree. The associated problem-solving technique in RPMT was described as the faculty of managing the hierarchy of goals and subgoals since each item has decomposable segments for pairwise comparisons (23). In summary, RPMT requires the conceptualization of relationships in advance from the very simple/concrete to the very complex/abstract, and also demands working memory, mental flexibility, category shift, problem solving, abstraction and reasoning (20). In this way, RPMT is considered a test evaluating the subjects' reasoning ability. The RPMT scores has been shown to correlate closely with the scores on test using different analogies such as number, verbal and geometric ones (25). For the present study first, third and fifth sections of RPMT were administered.

Visual Verbal Test

Visual-verbal test (VVT) has been used to evaluate the ability to formulate abstract concepts and the cognitive flexibility (26). Subjects are required to discern and abstract related attributes and pass over irrelevant ones. The original 42-item test was modified by Wicklund and it is reported that this abbreviated VVT provides a convenient measure of reasoning (27). In VVT individuals are asked to assess four simple geometric figures and choose three with common features. After the first one, they are asked to generate another trio with a different commonality. As an example, in item 2 there is four funnel: three upright makes a category and three empty one makes another. So, individuals make two different groups from the same four figures. Two scores are obtained from the 10 test items; each correct trio and each correct shift from one sort to another within the same series of figures awarded 1 point. Therefore, subjects get maximum 20 points from sorting, and 10 points from shifting. The total sort score provides a direct measure of ability to formulate abstract similarities and the shift score provides a measure of cognitive flexibility (27, 28).

Data Analysis

Data analysis was performed in IBM SPSS Windows Version 21.0 package program. Numerical variables are presented with mean±standard deviation values. The conformity of the numerical variables to the normal distribution was examined with the Shapiro Wilk Test, and the homogeneity of the variances was examined with the Levene test. For comparison of cognitive variables between the RRMS group and their respective control group a two-tail student t-test test was employed if the parametric test assumptions were met, otherwise Mann-Whitney U test if they did not. Multi-group comparisons were analysed with one way ANOVA test. Relationships between variables were evaluated with the Pearson correlation test. When $p<0.05$, the finding was considered statistically significant.

Results

There were 22 female and 8 male in the MS group and 21 female and 9 men in the control group. RRMS and control groups were not different in terms of gender, age and education level (Table 1). BDI and MMSE scores were similar in both groups (p: 0.957, and p=0.992 respectively).

Scores on neuropsychological tests evaluating working memory, attention and executive functions are given in Table 2. RRMS patients' performance on the TMT part A, B and PASAT were worse than the control groups. However, no difference was observed between persons with MS and healthy persons regarding RPMT performance. Also, in the same way, patients' performance on VVT components, total number of both sorts and shift, were similar to their healthy counterparts (Table 2).

When patients were grouped according to their onset symptoms as visual, motor, sensorial and cerebellar, no significant difference was observed for VVT and RPMT between groups (VVT, total sort F=0.499, p=0.686; VVT, total shift F=0.468, p=0.707; RPMT F=2.222, p=0.109).

To evaluate the burden of advanced age to analogical reasoning patient and control groups were divided in to three age groups. Healthy subjects had no statistically significant difference between age groups for any one of the test, however RRMS patients with advanced age exhibited a poor performance (Table 3).

In MS group RPMT scores showed an inverse weak-moderate correlation with disease duration (r=-0.354), though it was not at a statistically significant level (p=0.055). However, an inverse moderate correlation was observed between disease duration and both VVT-total sorts and shifts (r=-0.444, p=0.014 and r=-0.442, p=0.014, respectively). Neither RPMT nor VVT scores showed any statistically significant correlation with attack number and EDSS scores.

RPMT and VVT -total sorts and total shifts- showed a good correlation with tests evaluating executive functions (Table 4). Overall, the high scores on the PASAT, digit span forward and digit span backward tests correlated moderately or well with RPMT and VVT scores. The longer was the time to complete TMT-A, the lower was the scores on RPMT and VVT-total shifts. Higher was the scores on digit span and PASAT better was the RPMT and VVT performance (Table 5).

Table 1 Demographic data of patients and healthy controls

	MS	Control	p
Gender, F (%)	22 (73.3)	21 (70.0)	0.779
Age, yrs	31.13±7.77	30.70±8.50	0.837
Education, yrs	10.67±3.77	10.27±2.96	0.649
BDI	9.57±5.26	9.48±6.50	0.957
MMSE	28.10±1.35	28.10±1.45	0.992
Disease duration, m	62.20±52.70		
Attack number	3.13±1.91		
EDSS	1.38±1.32		

MMSE: Mini-Mental State Examination, EDSS: Expanded disability status scale, BDI: Beck Depression Inventory

Table 2 Mean test scores on neuropsychological test measures

		MS	Control	p
Trail Making Test-A (s)		51.23±29.86	34.27±10.57	0.005
Trail Making Test-B (s)		84.47±44.99	57.17±16.29	0.003
Digit span	Forward	9.90±3.07	11.07±2.52	0.113
	Backward	5.73±2.96	5.43±1.89	0.641
PASAT-3		25.70±13.16	35.11±13.61	0.013
Raven's Progressive Matrices Test		23.30±5.40	25.20±4.90	0.159
Visual-Verbal Test	Total sorts	18.13±2.32	17.64±4.05	0.570
	Total shifts	8.30±2.02	8.46±1.86	0.749

Table 3 Scores on working memory, attention and executive functions according to age subgroups (Values are given as Mean (SD))

	RRMS						Control				
Age (yrs)	**TMT-A**	**TMT-B**	**DS-f**	**DS-b**	**PASAT**	**EDSS**	**TMT-A**	**TMT-B**	**DS-f**	**DS-b**	**PASAT**
≤25	37.7 (13.1)	67.7 (12.6)	10.7 (2.2)	6.1 (3.3)	32.3 (8.5)	0.6 0.5)	31.9 (9.1)	51.8 (12.9)	11.6 (1.9)	6.6 (1.9)	41.8 (7.2)
26-35	41.5 (16.9)	72.7 (30.7)	10.9 (2.8)	6.9 (2.6)	37.5 (10.3)	1.7 (1.2)	30.9 (10.7)	54.4 (14.4)	11.3 (1.9)	5.6 (1.8)	41.6 (8.8)
≥36-49	81.2 (39.6)	121.2 (65.1)	7.2 (2.9)	3.1 (1.6)	18.2 (9.5)	2.5 (1.4)	41.3 (8.9)	65.7 (19.6)	10.2 (2.6)	4.1 (1.3)	30.9 (13.3)
ANOVA F(p)	8.376 (0.001)	4.584 (0.019)	5.243 (0.012)	5.899 (0.007)	9.695 (0.001)	5.891 (0.008)	3.373 (0.049)	1.933 (0.164)	0.749 (0.482)	4.9 (0.015)	3.309 (0.164)

TMT: Trail making test; DS-f: Digit span-forward; DS-b:Digit span-backward; EDSS: Expanded disability status scale

Table 4 RPMT and VVT total sort and shift scores according to age subgroups.

	MS			Control		
Age (yr)	RPMT	VVT-so	VVT-sh	RPMT	VVT-so	VVT-sh
≤25	23.50±4.12	18.50±1.64	8.67±1.51	26.75±5.68	19.33±0.52	9.33±0.52
26-35	25.44±4.95	18.94±1.61	9.00±1.46	24.62±4.57	18.23±1.92	8.23±1.92
≥36	18.88±4.80	16.25±3.01	6.63±2.50	24.66±4.92	15.67±6.52	8.22±2.27
ANOVA F(p)	5.054 (0.014)	4.603 (0.019)	4.813 (0.016)	0.528 (0.596)	1.841 (0.180)	0.827 (0.449)

Table 5 Correlation of reasoning and mental flexibility tasks with working memory, attention and executive functions

	TMT-A r (p)	TMT-B r(p)	DS-f r(p)	DS-b r(p)	PASAT r(p)
RPMT	-0.506 (0.000)	-0.342 (0.008)	0.351 (0.006)	0.491 (0.000)	0.727 (0.000)
VVT-sort	-0.265 (0.045)	-0.162 (0.224)	0.161 (0.229)	0.411 (0.001)	0.515 (0.000)
VVT-shift	-0.371 (0.004)	-0.235 (0.076)	0.391 (0.002)	0.425 (0.001)	0.540 (0.000)

Discussion

Analogical reasoning requires a mature cognitive processing capacity and faculty of grasping more developed strategies shaped by advancing age (9, 11, 12). Capacity of working memory, inhibitory control, and the faculty of drawing attention toward appropriate details and away from inappropriate ones are the main components of reasoning (11).

In this study we investigated the integrity of reasoning in patients with relapsing-remitting multiple sclerosis. The results showed that patients with RRMS had a similar performance to controls in discerning and abstracting relevant attributes and ignoring the irrelevant ones. Although they have salient attention and executive function deficits in comparison to controls they demonstrated intact abstract reasoning and cognitive flexibility skills. Amato et al found significant losses in abstract reasoning in patients with recent onset MS and low neurological disability; remaining substantially unchanged over 4 and 10 years (2, 4). In another one, performance on tasks requiring multiple abilities concurrently is reported to decline across time (29). Tuncer et al also reported RRMS patients achieving fewer conceptual categories and significantly greater number of perseverative responses in comparison to healthy controls (30). However, there are also several studies reporting normal visuospatial problem solving, abstract reasoning and set shifting abilities in relapsing-remitting MS patients; as was the case in our sample (31, 32). In our study, relatively young age, short disease duration and the low disability of MS patients may have hindered the presence of any significant difference in term of analogical reasoning.

Besides retrieval of appropriate real-world knowledge, an untainted working memory and executive functions are essential for a good performance in analogical reasoning. MS patients are known to exhibit some working memory impairment and executive dysfunction (29-33). Our small sample also had salient sustained attention, working memory and information processing speed deficits. In patient group RPMT and VVT-sort and -shift scores showed a positive moderate to strong correlation with PASAT and digit span, and a negative weak correlation with TMT-A and -B (Table4). These findings are compatible with the notion that the tests evaluating reasoning demand executive resources of working memory. However, a normal or good performance in reasoning tasks in the presence of impaired executive functions suggest that different neuroanatomical circuits are activated during these tests. Functional imaging studies revealed activation of the medial frontal, the left prefrontal, the anterior insula and the left inferior parietal cortices which are involved and activated during working memory, attention and executive function tasks (11,34,35) Functional connectivity analyses demonstrated that activation of pathways among these regions changes flexibly across cognitive processing in a task-dependent manner (36).

Analogical reasoning is driven by context-insensitive neural structures in the frontal cortex and context-sensitive neural structures outside the prefrontal cortex (9, 35). Rostrolateral prefrontal cortex and dorsolateral prefrontal cortex are activated during domain-independent relational reasoning, whereas, temporal, parietal and occipital cortex activations may flexibly vary depending upon the domain of mental representations within a given task and may differ according to the visual-spatial or verbal-semantic nature of the analogies (9,36-38). All these anatomical regions are involved in bottom-up perception and top-down control over representations related to reasoning; in specific the left rostrolateral prefrontal cortex mediates relational comparisons and enables remote searches for associations, bilateral dorsolateral prefontal cortex

along with parietal and occipital cortex support executive control networks, and medial frontal gyrus and left inferior frontal gyrus mediates inhibitory control for non-dominant meanings (9,11,35-38). MS demyelinating plaques may affect any or more of these neural networks to varying degress and may interfere processing and transfer of information required for analogical reasoning. The RPMT demands consolidation and processing of complex information but not activation and consolidation of relevant knowledge; and distraction is not systematically varied (23, 24). So, it might be thought that some MS patients may experience trouble with analogical reasoning; when they are required to recollect and integrate the relevant information or to hold out against interference (31). Hence it is likely that some MS patients might have analogical reasoning problems when compared to healthy controls. However, the performance of MS patients on the RPMT and VVT suggests that they can successfully manage to reason the relationally complex and abstract materials. Similar performance in the RPMT and VVT with healthy individuals found in this study shows that MS patients can reason by coping with relationally complex and abstract materials. However, it also reveals that the ability to grasp and express abstract similarities, and cognitive flexibility deteriorate with advancing age (Table 3, 4). The statistically significant detoriation with advancing age not only in relational reasoning ability but also in working memory and executive functions further support an impaired cognitive reserve capacity from the early stages of MS.

Cognitive deficits in MS patients correlate with lesion burden and atrophy detected in cranial magnetic resonance imaging. There are cross-sectional and longitudinal studies revealing moderate to strong correlations between the severity of cognitive impairment and total brain lesion burden; and implying lesion load as an important causal factor of cognitive impairment (2, 33). Executive dysfunction has been reported to be specifically associated with frontal lobe burden (33). Analogical reasoning was shown to activate medial frontal, left prefrontal as well as anterior insula and the left inferior parietal cortices in functional imaging studies (34, 38, 39). Although we did not evaluate the neuroimaging findings the presence of executive function impairment implies involvement of frontal- networks in our sample.

Small sample size may be considered a limitation of the study. However, persons with MS were relatively young with no cognitive complaints, a shorter disease duration, and lower disability. Also, those with any co-existent clinical conditions that might interfere cognitive functions were not included in the study. Selection of participants according to a stringent criteria may obviate the smallness of sample size as a limitation. Detection of significant cognitive dysfunction even in a group formed according to strict criteria, suggests that cognitive dysfunctions experienced and observed in MS patients in general are much more common. Absence of evaluations in the light of lesion burden on neuroimaging findings may be considered as another limitation. The findings were not included in the study because the neuroimaging studies evaluated in the MS patient group were performed in different centers and at different times. Since MS patients differ from each other in terms of clinical presentation, level of disability, anatomical location and number of demyelinating lesions, to set off a uniform group to assess the cognitive impairment poses a challenge in all MS studies. This heterogeneity also should be weighed in the evaluation of the results.

Conclusion

Cognitive dysfunction can be detected even in MS patients who are relatively young and have low disability, without any cognitive complaints. Although early cognitive reserves are sufficient for performance in analogical reasoning tasks similar to that of healthy controls, they show significant deterioration with advancing age.

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Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee was approved this study (07.03.2012/1064). The study was conducted in line with the principles of the Helsinki Declaration.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Authors can confirm that all relevant data are included in the article.

Authors Contributions

M.D.Ü: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

S.D: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

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