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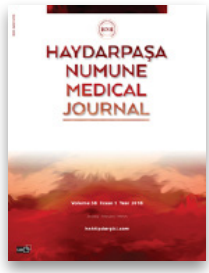

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ORIGINAL ARTICLE

A Comparison of Executive Functions in Normal Aging, Mild Cognitive Impairmant, and Early Stage Alzheimer Type Dementia in Turkish Sample

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Abstract

Introduction: In this study, neuropsychological profiles of Mild Cognitive Impairment (MCI) and early-stage Alzheimer's Disease (AD) were explored with a comprehensive neuropsychological battery that evaluates attention, memory, executive functions, language, visual-spatial, and behavioral skills.

Methods: In this study, 60 people with minimum primary school degree were included. Twenty people of those with early-stage AD (12 women, 8 men), while 20 people were with MCI (10 women, 10 men). These groups were matched for age, sex and education with 20 normal elderly subjects (9 female, 11 male).

Results: Our findings showed that the general cognitive profile of MCI is manifested as episodic memory and a semantic memory disorder. In contrast, in early-stage AD patients, language, visual-spatial skills, executive function, abstraction and interference resistance skills were found to be impaired and episodic and semantic memory problems were observed.

Discussion and Conclusion: The results of the present study suggesting a distinguished profile of MCI can be a promising factor in distinguishing the fine boundary between MCI and early-stage AD with an opportunity for early diagnosis and treatment of AD in the Turkish sample.

Keywords: Dementia; early-stagestage Alzheimer's disease; executive functions; mild cognitive impairment; normal aging.

The intermediate state between the normal aging process and dementia that does not meet the diagnosis of dementia clinically can be named as mild cognitive impairment (MCI). MCI is described with memory-related complaints or objective memory loss that is not in congruence with the age of the individual accompanied by completely healthy or not problematic other cognitive functions and activities of daily living are preserved. According to Petersen[1], MCI diagnostic criteria should consist of five factors: (1) the memory problem described by the patient him/herself, (2) determination of a memory defect based on the patient's age (the episodic memory score should be less than at least 1.5 standard deviations from normal scores), (3) normal cognitive functions (other than mem-

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ory), (4) maintenance of daily activities, and (5) not enough symptoms for clinical diagnosis for dementia.

There is an ongoing debate about the extent to which the non-memory areas, especially executive functions, can be considered for the diagnosis of MCI[2]. Other cognitive functions, such as language, verbal fluency, or naming, are more severely impaired in patients with MCI than in patients with stable deficiencies. Disturbance in attention and executive functions is an early and sensitive pre-vision tool for the transformation of MCI to more severe problems in the future[3]. Most people with MCI correspond to 0.5 points, which is suspected dementia according to the Clinical Dementia Rating Scale (CDR)[4-6].

Alzheimer's Disease is a progressive degenerative brain disease characterized by an abnormal accumulation of senile plaques and neurofibrillary tangles with neocortical atrophy, extensive loss of neurons, and synapses. Evidence suggests that these neurodegenerative changes usually occur first and most commonly in the hippocampus and entorhinal cortex then into the association cortices of the frontal, temporal, and parietal lobes[7]. At the same time, AD is a progressive brain disease that leads to extensive cognitive deficits, including memory, perception, attention, psychomotor and cognitive speed, visual-spatial functions, language, and intelligence[8].

Impairment in executive functions may occur in the early-stages of the disease. The executive dysfunction in AD refers to the impaired abilities that are responsible for proper use of knowledge, conceptualization, problem solving, and cue-directed behavior. Patients with mild dementia with AD are significantly unsuccessful in the tests requiring modification, self-monitoring, or sequencing compared with normal elderly subjects. For instance, in a study conducted by Bondi et al.[9] showed that the number of categories completed in Wisconsin Card Sorting Test (WCST) was a significant criterion for differentiating early-staged AD subjects and normal elderly subjects. Moreover, Petersen et al.[1] compared healthy controls with MCI patients, Pre-AD subjects (CDR 0.5), and early AD subjects (CDR 1) with various cognitive measures and as a result, all memory tests of MCI subjects (word list learning, paragraph learning and visual production) were reported to be significantly impaired compared to normal group and they were similar to those of AD group. However, the performance of the MCI group in other cognitive domains (such as naming, executive functions) was the same in healthy elderly controls.

In our study, early-staged cognitive Alzheimer's Disease, mild cognitive impairment, and normal subjects are aimed to be compared to determinate their cognitive profiles and for these three cases, determining the changes in executive functions formed our main research problems.

Materials and Methods

Participants

Sixty participants were included in this study. Twenty early-stage AD patients (12 women, 8 men) and 20 patients with MCI (10 women, 10 men) were matched for age, gender and education who applied to the dementia outpatient clinic (Istanbul University, Istanbul Faculty of Medicine, Department of Neurology, Behavioral Neurology Policlinics and Marmara University, Faculty of Medicine; Department of Neurology Polyclinics) with the ethical permission of the institutes. Diagnosed groups were compared with 20 normal elderly (9 women, 11 men). The diagnosis of the patients who formed the patient groups was made according to the relevant criteria by experienced clinicians in evaluating dementia and memory disorders. The subjects were required to be at least primary school graduates. In the selection of normal subjects, inclusion criteria were not to have any neurological, psychiatric and systemic diseases.

A neuropsychological evaluation battery was used in this study with a series of neuropsychological tests. Namely, for attention Number Range (Wechsler Memory Scale sub-test) test; for executive functions Wisconsin Card Sorting Test and Stroop Test; for verbal fluency Animal Counting Test and K-A-S; for abstract thinking, Binary Similarities Test, Interpreting Proverbs Test; and finally, for behavioral status Geriatric Depression Scale and Frontal Behavior Inventory were used in this study.

Tests were applied to each subject individually by the researchers. The participants were given information about this study before the application without giving clues about tests. The subjects and the experimenter worked alone in an environment that was purified in the best possible way from physical stimuli such as overheat, disturbing light, and sound. The Frontal Behavior Inventory was completed by discussing the subjects with an informant who is a relative of the patient.

Tests and different parts of the tests were applied in the following sequence: (1) Number Range Test, (2) Stroop Test, (3) Wisconsin Card Sorting Test, (4) Category fluency (animal), (5) Phonemic fluency (K-A-S), (6) Binary Similarities, (7) Interpreting Proverbs, (8) Geriatric Depression Scale, (9) Application of Frontal Behavior Inventory to the patient.

Results

Significance levels were calculated using a one-way analysis of variance (One-Way ANOVA) to look at the difference between age and education variables in AD, MCI and normal groups. The level of significance was accepted as .05. The data obtained by the neuropsychological tests used in our study showed a non-normal distribution in groups of AD, MCI and normal subjects. Therefore, in the comparison analysis between the groups, non-parametric equivalents of the parametric tests (one-way ANOVA and t-test), namely, the Kruskal-Wallis Test and the Mann-Whitney-U Test were preferred.

For age and education, AD, MCI and normal groups were compared with ANOVA Test, and no significant difference was found between the groups ($F(2, 57)=0.56$, $p<0.05$; Table 1).

In all scales, AD, MCI and normal groups were firstly compared with Kruskal-Wallis test and if the difference was found as statistically significant in those three groups, Mann-Whitney U test was used to determine that which two groups had that difference (Table 2).

Discussion

In our study, neuropsychological evaluations were used to determine the cognitive profiles of early-stage AD, MCI and normal cases and it was aimed to see the changes in the executive functioning of these three groups.

We used the Numerical Range Test to evaluate simple attention. The findings showed that early-stage AD group was different from only the normal group in the straight numerical range but different from both the MCI group and the normal group in the backward numerical range. There are different interpretations in the literature on this finding. Öktem[10] states that attention distortion in patients with early-stage AD occurs in the form of deterioration in complex attention rather than simple attention with emphasizing that simple attention, measured by forward and reverse number-range tests, is maintained. Attention impairments, especially sustained in AD and selective attention, could be used as an indicator for AD[11]. Berardi et al.[12] showed that AD patients had lower performance on concentrating both automatic and effortful tasks. Besides AD patients, the possible AD patients showed impairments in a selective attention task. Weintraub[13] notes that attention deficits may sometimes be seen in early-stage AD or may occur even before memory impairment. In concordance with this, a simple attention deficit was detected in the AD group in our study. Also, the performance of the AD group in the reverse number range test was significantly lower than MCI and normal groups. Lezak[14] argues these tests to be considered as two different test formats: forward number range as an attention test and backward number range as working memory test. We think that the problems in the backward number range achieved in our study are related to this explanation. Our findings are also consistent with the results of a study conducted in Turkey[15] wherein the forward number range in the AD group is within normal limits compared to normative values, while the backward number range is seen to be below up to 1.5 standard deviations.

Table 1. Age and education descriptive statistics for AH, MCI, and normal group

Variable	N	Median	SD	Min.	Max.
Age					
AD	20	74.35	5.17	68	90
MCI	20	73.05	7.20	52	84
Normal	20	72.20	6.86	57	87
Education					
AD	20	9.90	3.54	5	15
MCI	20	12.20	3.97	5	20
Normal	20	11.15	4.12	5	19

In our study, executive functions, namely, rule finding, category creation and category change, were evaluated using Wisconsin Card Sorting Test, and patients with AD had a significant difference compared to the normal group in these categories that were completed. Although MCI patients showed normal performance, a statistically significant difference was found when compared to the results of the normal group of our study. This was because the normal group had exceptionally high performances. There was no significant difference in the number of perseverative responses, percent of perseverative error, number of trials used to complete the first category, and percentage of conceptual level response between the MCI patients and the normal group in the detailed evaluation. However, patients with MCI were unsuccessful in maintaining the setup compared to the normal group. We think this finding can be explained by the argument that maintaining the setup is related to attention. In addition, in a study[16] using factor analysis employing the Wisconsin Card Sorting Test, it was concluded that perseveration scores were the most important parameters and they were directly related to dorsolateral prefrontal cortex function. Therefore, perseveration scores are the number one parameter corresponding to executive functions. From this direction,

Table 2. Result of Mann-Whitney U test for AH, MCI and normal participants

Variable	Group	n	Rank Mean	Rank Sum	U Test	p
Wechsler Memory Scale						
Number Range	AD	20	17.20	344.00	134.00	0.054
	MCI	20	23.80	476.00		
	AD	20	15.28	305.50	95.50	0.002
	Normal	20	25.73	514.50		
	MCI	20	18.35	367.00	157.00	0.192
	Normal	20	22.65	453.00		
Reverse Number Range						
	AD	20	13.60	272.00	62.00	0.000
	MCI	20	27.40	548.00		
	AD	20	12.78	255.50	45.50	0.000
	Normal	20	28.23	564.50		
	MCI	20	18.73	374.50	164.50	0.292
	Normal	20	22.28	445.50		
Verbal Fluency Test						
Animal Counting	AD	20	15.30	306.00	96.00	0.005
	MCI	20	25.70	514.00		
	AD	20	10.85	217.00	7.00	0.000
	Normal	20	30.15	603.00		
	MCI	20	16.25	325.00	115.00	0.021
	Normal	20	24.75	495.00		
Animal Counting Perseveration	AD	20	25.38	507.50	102.50	0.006
	MCI	20	15.63	312.50		
	AD	20	28.05	561.00	49.00	0.000
	Normal	20	12.95	259.00		
	MCI	20	23.65	473.00	137.00	0.024
	Normal	20	17.35	347.00		
K.A.S. Fluency	AD	20	15.03	300.50	90.50	0.003
	MCI	20	25.98	519.50		
	AD	20	13.45	269.00	59.00	0.000
	Normal	20	27.55	551.00		
	MCI	20	18.60	372.00	162.00	0.304
	Normal	20	22.40	448.00		
K.A.S. Fluency Perseveration	AD	20	22.83	456.50	153.50	0.177
	MCI	20	18.18	363.50		
	AD	20	25.60	512.00	98.00	0.002
	Normal	20	15.40	308.00		
	MCI	20	22.90	458.00	152.00	0.107
	Normal	20	18.10	362.00		
WAIS-R						
Binary Similarities	AD	20	10.58	211.50	1.50	0.000
	MCI	20	30.43	608.50		
	AD	20	10.58	211.50	1.50	0.000
	Normal	20	30.43	608.50		
	MCI	20	19.45	389.00	179.00	0.494
	Normal	20	21.55	431.00		
Proverbs	AD	20	20.13	402.50	192.50	0.789
	MCI	20	20.88	417.50		
	AD	20	20.25	405.00	195.00	0.858
	Normal	20	20.75	415.00		
	MCI	20	20.63	412.50	197.50	0.928
	Normal	20	20.38	407.50		

Table 2. CONT.

Variable	Group	n	Rank Mean	Rank Sum	U Test	p
Stroop Test						
Time Difference	AD	20	25.88	517.50	92.50	0.004
	MCI	20	15.13	302.50		
	AD	20	27.98	559.50	50.50	0.000
	Normal	20	13.03	260.50		
	MCI	20	24.55	491.00	119.00	0.028
	Normal	20	16.45	329.00		
False	AD	20	29.18	583.50	26.50	0.000
	MCI	20	11.83	236.50		
	AD	20	30.00	600.00	10.00	0.000
	Normal	20	11.00	220.00		
	MCI	20	23.00	460.00	150.00	0.019
	Normal	20	18.00	360.00		
Spontaneous Correction	AD	20	27.25	545.00	65.00	0.000
	MCI	20	13.75	275.00		
	AD	20	29.50	590.00	20.00	0.000
	Normal	20	11.50	230.00		
	MCI	20	25.13	502.50	107.50	0.011
	Normal	20	15.88	317.50		
WCST						
Completed Category Number	AD	20	12.68	253.50	43.50	0.000
	MCI	20	28.33	566.50		
	AD	20	10.50	210.00	0.00	0.000
	Normal	20	30.50	610.00		
	MCI	20	16.88	337.50	127.50	0.007
	Normal	20	24.13	482.50		
Perseveration Reaction Number	AD	20	26.80	536.00	74.00	0.001
	MCI	20	14.20	284.00		
	AD	20	29.83	596.50	13.50	0.000
	Normal	20	11.18	223.50		
	MCI	20	23.70	474.00	136.00	0.083
	Normal	20	17.30	346.00		
Perseveration Fault Percentage	AD	20	26.78	535.50	74.50	0.001
	MCI	20	14.23	284.50		
	AD	20	29.23	584.50	25.50	0.000
	Normal	20	11.78	235.50		
	MCI	20	21.55	431.00	179.00	0.570
	Normal	20	19.45	389.00		
First Category Completed Used Test Number	AD	20	25.78	515.50	94.50	0.004
	MCI	20	15.23	304.50		
	AD	20	26.03	520.50	89.50	0.002
	Normal	20	14.98	299.50		
	MCI	20	19.75	395.00	185.00	0.669
	Normal	20	21.25	425.00		
Conceptual Reaction Level Percentage	AD	20	13.10	262.00	52.00	0.000
	MCI	20	27.90	558.00		
	AD	20	10.68	213.50	3.50	0.000
	Normal	20	30.33	606.50		
	MCI	20	17.38	347.50	137.50	0.091
	Normal	20	23.63	472.50		

Table 2. CONT.

Variable	Group	n	Rank Mean	Rank Sum	U Test	p
Setup Prolongation Failure	AD	20	24.85	497.00	113.00	0.012
	MCI	20	16.15	323.00		
	AD	20	27.68	553.50	56.50	0.000
	Normal	20	13.33	266.50		
	MCI	20	24.05	481.00	129.00	0.008
	Normal	20	16.95	339.00		
Geriatric Depression Scale						
Geriatric Depression Scale	AD	20	24.45	489.00	121.00	0.032
	MCI	20	16.55	331.00		
	AD	20	27.48	549.50	60.50	0.000
	Normal	20	13.53	270.50		
	MCI	20	23.98	479.50	130.50	0.058
	Normal	20	17.02	340.50		
FBI						
FBI Negative	AD	20	25.78	515.50	94.50	0.004
	MCI	20	15.23	304.50		
	AD	20	30.50	610.00	0.00	0.000
	Normal	20	10.50	210.00		
	MCI	20	30.00	600.00	10.00	0.000
	Normal	20	11.00	220.00		
FBI Disinhibition	AD	20	23.88	477.50	132.50	0.067
	MCI	20	17.13	342.50		
	AD	20	30.00	600.00	10.00	0.000
	Normal	20	11.00	220.00		
	MCI	20	30.00	600.00	10.00	0.000
	Normal	20	11.00	220.00		
FBI Total	AD	20	25.18	503.50	106.50	0.011
	MCI	20	15.83	316.50		
	AD	20	30.50	610.00	0.00	0.000
	Normal	20	10.50	210.00		
	MCI	20	30.00	600.00	10.00	0.000
	Normal	20	11.00	220.00		

our findings showed that AD patients differed significantly from both MCI patients and the normal group, and there was no difference between MCIs and normal group. Compared to the scores reported in the BILNOT battery[17], the scores of the patients with AD in our study were below the norms but not reaching 1.5 standard deviation below. A study[18] compared plasma tau levels and cognitive functions in mild cognitive impairment and early Alzheimer's disease, the findings showed that plasma tau levels were higher both in MCI and early AD patients. As associated with the participants' WCST performance, plasma tau levels were positively significant and gray matter densities in hippocampus, amygdala and various regions were negatively significant in MCI and AD patients. Early AD patients had a lower performance than MCI patients, and MCI patients had a lower performance on WCST than healthy control. These results suggest that the prefrontal cortex functions, which can be argued as being protected in patients with early-stage AD in the literature, is still partially preserved, but at this stage, it is thought to be starting to be affected.

The Stroop Test was used to evaluate the ability to inhibit inappropriate response. In this test, the findings showed that the normal group was more successful than the MCI patients and the MCI patients were more successful than the patients with AD. This difference was determined for all three sub-variables -namely, interference time, errors and spontaneous corrections-. Although the results of MCI and normal groups showed a statistically significant difference, they were quite close to each other. Another study[19] examining the comparison of AD, MCI and healthy aging using the Stroop task showed that even both MCI and AD patients had severe impairments in inhibition task; AD patients had lower performance. As seen in our study, literature findings[19,20] also revealed that resistance to inter-

ference is increasingly impaired in the later stages of the disease. When compared with the results of the study on normal subjects in Turkey[21], it was seen that the duration of interference, the number of errors and the number of spontaneous corrections in AD patients differ from the normative values up to 1.5 standard deviations. Moreover, patients with MCI showed a slightly lower performance than normative values. It can be said that the main neural infrastructure of the interference resistance test is the orbitofrontal cortex. When the progression of neurodegeneration in AD is considered, it is expected that this paralimbic cortex will be privileged in the prefrontal cortex. Therefore, we believe that the poor performance in the Stroop test can be explained by this anatomical predisposition.

Verbal fluency was evaluated by Animal Counting and K.A.S. tests. In animal counting test, AD patients showed lower performance than MCI and normal groups. Phonemic fluency in the MCI group was not impaired based on the normal groups, whereas animal counting requiring the preservation of semantic information significantly affected. This situation suggests that semantic information is also affected by MCI cases, as defined in the literature[7]. For instance, Cooper et al.[22] applied the semantic fluency test (animal counting) to AD, amnestic MCI patients, and normal group two times with a one-week interval. It was observed that the normal group increased their performance in repeated tests; however, patients with MCI did not improve their performance, as well as the AD group. This situation is similar to our findings, which suggest that MCI patients are close to the AD group rather than the normal group in terms of semantic fluency. In another study[23], researchers examined different verbal fluency tests (category and phonemic fluency) on AD patients and compared them with normal controls. In all verbal fluency tests, they found that category fluency was the most distinctive area with high precision. They explained that the fluency of the category has a more pronounced and earlier deterioration than other tests due to its semantic information structure. In the study of Moncsh[24], they argued that the deterioration in category fluency showed the loss of semantic information in the early-stages of AD. When compared with the results of the study on normal subjects in Turkey[21], it can be seen that according to the normative values in Turkey, categorical word fluency decreased in both AD and MCI patients, whereas phonemic fluency is below the norms only in AD patients, but a 1.5 standard deviation difference did not exist.

There was no significant difference between the groups in the "Interpretation of Proverbs" evaluating thinking skills in abstract. When we examine the literature, since proverbs are well-learned conceptual expressions, they are not expected to be impaired in their interpretation in the early period of disorders[10]. In our study, this argument was supported, and Interpretation of Proverbs has been preserved in both MCI and AD patients. However, another study[25] found that the impairment of proverb interpretation was less in MCI patients compared to early AD patients, but not significantly. In addition, Leyhe et al.[26] examined amnestic MCI and early AD in proverb interpretation as a representative of executive functioning: amnestic MCI and early AD patients had more impairment than healthy controls, also early AD patients had given more meaningless answers.

Likewise, in the Binary Similarity Test which evaluates abstraction skills, results deteriorate from the early-stages of AD as patients tend to find more concrete similarities instead of basic and abstract similarities. In accordance with this, in our study, it was observed that there was a significant deterioration in the AD group when three groups compared with each other, but there was no difference between the MCI group and the normal group. Although Binary Similarity Test is accepted as a test which evaluates abstraction ability, to show better performance, it is needed to find out upper semantic category which two objects belong to in the same category. Innately, on one hand, it is abstraction while on the other hand language functions and semantic memory that should be optimum. It can be argued that AD group has impairments in both areas as binary similarity impairment is more related to a language function and semantic memory response than abstraction impairment. At least, we can state that it cannot be argued to be only abstraction impairment.

Patients with depression were excluded from our study for evaluating cognitive performance independently from other factors. In that purpose, although significant differences between groups were found between AD, MCI, and normal groups in their Geriatric Depression Scale scores, none of them were severe enough for a depression diagnosis. However, expectedly, scores were higher in AD patients that can be evaluated as having an insight about the disease that is not impaired yet at the early-stages of AD.

Frontal Behavior Inventory was applied to the patients' relatives to evaluate their behavioral problems. Some of the normal subjects' relatives could not be reached for the questionnaire; thus, this scale could not be completed for them. Therefore, only AD and MCI groups were compared concerning negativism, disinhibition and total behavior scores. The findings showed that while total behavioral

scores had a statistically significant difference between AD and MCI groups, behavioral disinhibition scores did not have statistically significant difference. AD group had severely significant behavioral change than the MCI group. This finding is thought to be due to our results' support for the statement that in the MCI group, only the limbic system structure is affected, but in the AD group, additionally, limbic system's prefrontal influence is starting. We argue that the reason beyond it was there is no found difference between disinhibition scores at the early-stage is the lack of behavioral problems in that stage.

As a result, in our study, MCI's general cognitive profile showed episodic and semantic memory impairment. Gomar[27] compared working memory and executive functions in MCI, AD, and healthy controls. The findings showed that AD patients have significantly more impairment than MCI, while MCI patients were significantly worse than healthy controls. Attentional set-shifting, working memory and cognitive control were common deficits and impairments in some of these tests for MCI patients, which were explained as their possible episodic memory impairment. On the contrary, AD patients often had episodic and semantic memory impairments accompanying language, visuospatial scratch ability and some of executive functioning impairments. All groups comparisons show that all executive functions demonstrate the statistically significant differences with the AD group being disadvantageous. However, when AD group's mean scores were evaluated with the normative scores in the literature concerning executive function scores -except Binary Similarity and Stroop Test interference time, false, and spontaneous correction-, it was observed that the criteria of individual evaluation of impairment's at least one standard deviation below the normative value did not meet. Those results are congruent with the hypothesis mentioned before stating prefrontal heteromodal, which is the neural substructure of executive functioning, is not impaired by the loadings of the posterior heteromodal cortex at the early-stages of AD yet.

In our study, we observed that MCI patients showed different performances for semantic fluency, which made us argue that patients with MCI whose semantic network was not degenerated yet like the others in the same spectrum can be argued to be close to normal, while other patients with MCI with apparent impairment are closer to the AD group of whom prefrontal limbic degeneration starts very early. For future studies, using larger groups of patients with MCI diagnosis may enable researchers to examine semantic fluency performance preceding the inclusion of the patients with impaired semantic fluency performance to the group of AD diagnosis, while others included to the normal group. We believe that this information can be a promising factor in distinguishing the fine boundary between MCI and early-stage AD with an opportunity for early diagnosis and treatment of AD. Lastly, the impairment in sleep may be a risk factor for developing AD, and sleep problems may lead to attention deficits. In this context, it can be helpful to examine sleep problems of MCI and AD patients to explain the dynamics behind their attention deficits rather than evaluating it as related to depression only[11].

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