

Original Research Article

# Lexical Retrieval or Semantic Knowledge? Which One Causes Naming Errors in Patients with Mild and Moderate Alzheimer's Disease?

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## Keywords

Alzheimer's disease · Anomia · Conceptual knowledge · Lexical retrieval · Semantic layer · Phonological layer

## Abstract

**Background:** The purpose of the study was to analyze naming errors in patients with Alzheimer's disease in comparison to healthy subjects and determine the underlying cause of naming errors in these patients. **Method:** In this study, we included 35 healthy elderly subjects, 23 patients with mild Alzheimer's disease, and 23 with moderate Alzheimer's disease. Forty-five images were used to determine the type of naming errors, and to identify the underlying cause of errors, matching an image with a written word was used. **Results:** Patients with Alzheimer's disease had more naming errors compared with the group of healthy elderly, and patients with moderate Alzheimer's disease showed a slower reaction in matching an image with a written word. **Conclusion:** Anomia in the initial phase of Alzheimer's disease is due to problems in lexical retrieval; however, as the disease advances, in addition to lexical retrieval problems, conceptual knowledge causes naming problems.

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## Introduction

Alzheimer's disease is a progressive disorder of the nervous system of which the most common characteristic is persistent and progressive cognitive dysfunction, and the most common way of its emergence is amnesia [1]. Early symptoms of disease include progressive reduction of episodic memory, having trouble learning new things, loss of cognitive function,

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and especially linguistic deficits. One of the most important symptoms of Alzheimer's disease is progressive disorder in linguistic function [2]. Naming disorders may be the most important and obvious symptom in the initial phase of disease among all linguistic disorders in patients with Alzheimer's which may differ in nature over the course of the disease in a way that naming errors are different in terms of quantity and quality [3].

Naming is considered to be an important linguistic skill in interpersonal communications which summarily includes conceptualization, linguistic formulation, and articulation. The first step is representing the concept. This representation includes the information that an individual knows about that concept which is the mental image, semantic features, and its function [4]. Linguistic formulation or lexical access has two steps, the first step is to choose lemma, the second step is to choose the phonological features of intended concept which are phonological coding, choosing the number of syllables, phonemes, and the weight of target word. Naming problems can be due to deficits in any of these steps [5]. Studies related to naming are very important as anomia suggests the progress of the disease and the whole-brain atrophy [3].

Although naming deficits are early symptoms of Alzheimer's, and in some patients naming disorders are the main problem of speech [6], there is little information on that [7].

On the other hand, naming problem is a common complaint among the healthy elderly [2]. Results of studies on the healthy elderly show that naming problems in this group are not due to deficits in conceptual knowledge, and the only change is in lexical access [6], while naming problems in patients with Alzheimer's are due to deficits in concept [8].

In case this is true, examining the number and type of naming errors, it is possible to differentiate between these two groups. Perhaps the naming error patterns may be used clinically to distinguish healthy elderly people from patients with mild naming disorders due to Alzheimer's disease [9]. However, the error patterns alone cannot determine the cause of fundamental naming disorders, and the underlying cause of naming problems in Alzheimer's disease is still unclear. While results of some studies consider conceptual knowledge deficits as the origin of naming problems in patients, other studies focus on problems in phonological access of the lexicon or problems in other phases of lexical retrieval in these patients [3, 10–12].

To study the origins of naming problems in patients with Alzheimer's disease, a study was conducted on 10 patients testing them twice within 6 months. The results of the study showed that 81% of those words which had problems of retrieval in the first test, were not named in the second test as well, and naming errors were stable. The stability of naming errors is due to conceptual knowledge deficits and not the lexical access [13]. However, results of a study on a patient with Alzheimer's disease for 2 years showed that the patient is able to understand 75% of what he could not name in the naming test; therefore, the reason for anomia in this patient is considered to be due to deficits in lexical access [10].

Results of another study comparing a healthy group with patients with Alzheimer's in case of naming errors showed that the number of errors and no-response were far more in patients with Alzheimer's rather than healthy group. Based on results, it is reported that errors of patients with Alzheimer's are due to progressive destruction of conceptual knowledge, and the errors of the healthy elderly and patients with Alzheimer's are different in terms of quantity but the same in terms of quality [2].

In one study, naming errors were studied in three groups of patients with mild Alzheimer's, patients with moderate Alzheimer's, and the healthy elderly. The results of the study showed that as the disease developed, the number of naming errors increased. In the group of patients with moderate Alzheimer's, the number of unrelated naming errors and visual errors were more than the other two groups, and pattern of errors was not fixed comparing with the other two groups. Researchers concluded that an increase in number of no-response cases in the middle stage of disease may be associated with deficits in conceptual knowledge [3].

Contradictions in the cause of naming errors in patients with Alzheimer's can be due to the fact that these studies are only conducted on people with Alzheimer's or it can be because of not considering different levels and severity of the disease except for the study of Silagi et al. [3]. In the other words, type of naming errors, how deficits change during the disease, and nature of these naming problems in patients with Alzheimer's are still debated, and there is a need for further study [3, 14].

### Present Study

Increase in growth of the elderly population will be along with the unwanted occurrence of disorders related to age, such as Alzheimer's. Alzheimer's is also the most common cause of dementia in the elderly. Based on the data, it is estimated that 24.3 million people suffer from dementia and 4.6 million new cases of dementia are adding per year, in other words one case is adding in each 7 s. Although the number of patients with Alzheimer's in Iran is not definite, it is certainly growing as well; therefore, studying the problems of this group of people is highly important [15]. One of the most important problems of patients with Alzheimer's is naming disorders. The main objective of the present study is to provide evidence for naming disorders and its cause in patients with Alzheimer's disease. Some researchers believe that naming error patterns may have the potential to be used clinically to distinguish the healthy elderly from those patients with mild naming disorders due to Alzheimer's disease [9]. Besides, naming tests are simple neurologic tools which reveal several aspects of knowledge storage methods in human mind [2].

In fact, the main purpose of this study which was done in Farsi for the first time, is responding to inconsistencies in naming disorders and its nature in people with Alzheimer's. A comparison between the number and type of errors in three groups of healthy elderly, patients with mild Alzheimer's, and patients with moderate Alzheimer's has been done in this study, and also investigating the cause of the basic problem in naming disorders has been done through the assignment of matching unnamed items with their written form in these three groups. Since speech and language pathologists play an important role in the treatment of naming problems, the results of the study can be effective in improving the quality of treatment in these patients.

To describe the errors better and also to determine their nature, the interactive two-step model is used in the present study. Interactive two-step model is a lexical production model which is derived from the Spreading Activation theory. Based on this theory, linguistic units are retrieved as the activity in a layered network expands. Since in lexical access, there are two stages of phonological and semantic steps, this model is called a two-step model. It is also called interactive, because all connections between stages are two-way connections, and there are activities between these layers [16]. The three layers are semantic layer, lexical layer, and phonological layer. These layers create a regional representation which is consistent with linguistic units. Based on this model, the error may be made in the stage of phonological or lexical retrieval. In lexical retrieval, initiated activity spreads through network, and simultaneously with the activation of the lexical units of the target word, units around the target word are activated as well. In this case, words semantically close to the target word may be activated by mistake. In the stage of phonological retrieval, those units with most activities are selected. Choosing phonemes is based on the units which have been activated in lexical retrieval, otherwise phonological errors happen [17]. There is noise in this model too. Noise is made due to the of activity close nodes with the same meaning.

Description of errors based on the model and characterizing the problematic stage of naming can help therapists select an appropriate therapeutic approach. Since speech and

language pathologists play an important role in the treatment of naming problems and due to the fact that efficient studies suggest treatments for naming deficits in patients with Alzheimer's, the results of the study can improve the quality of treatment in these patients [16].

## Materials and Methods

### *Participants*

Participants in this study included 35 healthy elderly subjects, 23 patients with mild Alzheimer's and 23 patients with moderate Alzheimer's disease. All participants voluntarily completed a consent form, and all were selected from the center of geriatrics of Isfahan. All participants were native Persian speakers over 60 years old. They had no history of drug and alcohol abuse, and also there was no neurological and psychiatric disease (Alzheimer's patients before the onset of symptoms) as well as vision and hearing problems which affect cognitive skills. All participants were literate and were divided into groups of primarily literate, having diploma, or highly educated based on Iran educational system. Owing to the effect of education and age on cognitive tasks, the three groups were compared in these regards, and no significant difference was observed ( $p > 0.05$ ).

Alzheimer's patients who were previously diagnosed with Alzheimer's were selected from hospitals in Isfahan University of Medical Sciences. They ranged from mild (1) to moderate (2) according to Clinical Dementia Rating (CDR) developed by neurologists. The CDR is a 5-point scale used to characterize six domains of cognitive and functional performance applicable to Alzheimer's disease and related dementias: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. Severity ratings range along a 5-point scale (except for the personal care domain): CDR-0: no cognitive impairment, CDR-0.5: questionable or very mild dementia, CDR-1: mild, CDR-2: moderate, CDR-3: severe [18]. In order to assess cognitive status in the elderly healthy, the same scale was used and the score was equal to zero.

Table 1 shows sociodemographic characteristics of the participants.

In this study, 45 pictures of common nouns were used. These pictures were selected from naming test including 272 pictures. Selected words had more than 90% of name agreement [19]. Among these 45 pictures, 5 pictures were related to educating patients and 40 pictures were related to the evaluation. To show the pictures, software provided by Ghasisin and colleagues was used. The software was developed using C++ programming language and it is able to record voices and details of each person and keep them in a separate file. In case there is a pause, the software has the option to continue from where the test stopped [19]. Each picture was shown on monitor for 20 s [3] and sorting pictures was in a way that same semantic and phonological classes could not be together.

### *Procedure*

Participants were tested individually. First necessary instructions were given on how to respond, and the participants were asked to say the first name that comes to mind after looking at the picture. Five simple pictures were used to train the participants. During the test, all participants were accompanied by examiners who did not comment on their responses at all. After recording participants' voices, their responses were analyzed. Participants' responses were assessed to determine the number and type of errors by two independent assessors who had no information about the participants. Inter-rater agreement was more than 98% between assessors. Analyzing participants' responses to naming, correct answers were marked by 1 and errors were marked by 0, and a total score was calculated for each

**Table 1.** Sociodemographic characteristics of the subjects

Groups	Gender		Education			Age, years		
	female	male	primarily literate	diploma	highly educated	min	max	mean ± SD
Normal adult	21 (60%)	14 (40%)	10 (28.6%)	18 (51.4%)	7 (20.9%)	61	80	68.86±6.2
Mild Alzheimer	10 (43.4%)	13 (56.6%)	13 (11.7%)	6 (59.1%)	4 (21.4%)	60	83	70.57±6.97
Moderate Alzheimer	11 (47.8%)	12 (52.2%)	12 (52.17%)	9 (39.13%)	2 (8.7%)	62	83	71.35±5.58

participant. The errors were identified then. According to Philadelphia Naming Test (PNT) instructions, naming errors were classified into different types of errors such as semantic error, phonological error, blend error, naming part of a picture, repeating the previous response, circumlocution, no response, mixed, and other errors like unrelated errors [20]. In this study, in addition to mentioned errors in Philadelphia classification, some other types of errors were added to the study which are I know but I cannot remember, and visual errors.

In order to determine whether there is an impairment in conceptual knowledge or in lexical access, if participants made an error while naming a picture, they were asked to match the picture with the written form of it after the test of naming. Word-picture matching was tested in all errors.

For assessment, the procedure established by White-Devine et al. [21] was used here; the picture that error occurred in was matched with 4 writing formations. The four forms of writing had these features. One was correct item, the other one was the writing form of an picture that was selected with the target picture of a semantic class but was not in relation in terms of the written form with the target word, the latter was in the form of a written form similar to the target word but not semantically, in the end a word, which had no semantic relationship and written similarity to the word. In this assignment, in case the participants could recognize the right written word before 20 s, the score was 1, otherwise the score was 0. A total score was calculated for each participant at the end.

For the purpose of statistical analysis and due to abnormal responses of participants, the Kruskal-Wallis test was used to compare the naming performance (correct responses and errors), and the Mann-Whitney U test was used to compare the groups of the healthy elderly, patients with mild Alzheimer's, and patients with moderate Alzheimer's. Significant level is considered to be 0.05.

## Results

Types of errors in both groups are shown in Table 2. Accordingly in the moderate phase of disease, there is a decrease in the number of correct answers, an increase in the number of errors, and types of errors are changing. In assessment of the frequency of errors in three groups, the most common type of error in the healthy elderly and patients with mild Alzheimer's is semantic error, and in patients with moderate Alzheimer's, the common error is no response error (see Table 2)

Data analysis shows that there was a significant difference in correct responses, all errors, no response errors, semantic errors, non-word errors, unrelated errors, circumlocution, blend, and mixed errors between all groups of participants; however, in case of formal errors, no remember errors, visual, and also perseveration errors, there was no significant difference between groups (Table 3).

**Table 2.** Percentages of correct answers and type of errors in each group

Naming performance	Normal aging (n = 35)	Mild Alzheimer (n = 23)	Moderate Alzheimer (n = 23)
Correct answers	98%	93%	70%
No response	0.71%	1.20%	10.54%
Semantic	1.07%	2.40%	6.25%
Non-word	0%	0.70%	1.73%
Formal	0%	0.10%	0.10%
Perseveration	0%	0.10%	0.65%
Mixed	0%	0.7%	1.37%
Blend	0%	0.33%	0.54%
Circumlocution	0%	0.33%	4.23%
No remember	0%	0.22%	0.20%
Unrelated	0%	1.09%	3.80%
Visual	0.07%	0.11%	0.11%

**Table 3.** Naming performance in three groups and significant differences between the groups according to the nonparametric Kruskal-Wallis test

Naming performance	Normal aging (n = 35), mean rank	Mild Alzheimer (n = 23), mean rank	Moderate Alzheimer (n = 23), mean rank	Statistics and p value (df = 2)
Correct answers	59.6	40.2	13.3	$\chi^2 = 55.4; p < 0.001$
Total errors	22.3	41.8	69.6	$\chi^2 = 55.4; p < 0.001$
No response	29.9	34	64.8	$\chi^2 = 40.5; p < 0.001$
Semantic	27.5	38.3	64.2	$\chi^2 = 37.6; p < 0.001$
Non-word	32	43.7	52	$\chi^2 = 30.8; p < 0.001$
Formal	40.1	40.8	41	$\chi^2 = 19.9; p = 0.8$
Perseveration	40	41.7	41.7	$\chi^2 = 45.03; p = 0.46$
Mixed	30.5	42.8	55.1	$\chi^2 = 6.03; p < 0.001$
Blend	37	42.2	45.8	$\chi^2 = 1.54; p = 0.02$
Circumlocution	31	35.7	61.8	$\chi^2 = 26.8; p \leq 0.001$
No remember	39.5	42.9	41.3	$\chi^2 = 7.6; p = 0.2$
Unrelated	30	41.2	41.2	$\chi^2 = 2.9; p < 0.001$
Visual	30.1	32.1	32.8	$\chi^2 = 0.12; p = 0.3$

The Mann-Whitney U test was used to determine between which groups there were differences. Results of the test showed that in one category the difference is between the group of the healthy elderly and patients with mild and moderate Alzheimer's, and in another category, the difference is between patients with mild Alzheimer's and moderate Alzheimer's (Tables 4–6).

Table 7 shows the percentage of matching in any type of error in all three groups in which all healthy elderly were totally able to match the written word they had error in with its picture. In mild Alzheimer's, the only case in which there was not a match between the written word and its picture, was no response error; however, in moderate Alzheimer's, unrelated, circumlocution, non-word, and no response errors did not match.

There was a significant difference between the three groups according to the Kruskal-Wallis test ( $\chi^2 = 52.5, df = 2, p < 0.05$ ), and the Mann-Whitney U test showed that the healthy

**Table 4.** Naming performance in healthy aging and patients with mild Alzheimer disease and significant differences according to the nonparametric Mann-Whitney test

Naming performance	Normal aging ( <i>n</i> = 35), mean rank	Mild Alzheimer ( <i>n</i> = 23), mean rank	Statistics and <i>p</i> value
Correct answers	36.6	18.5	$z = -4.1; p < 0.001$
Total errors	22.1	40.4	$z = -4.1; p < 0.001$
No response	28.20	36.48	$z = -0.96; p = 0.03$
Semantic	26.2	34.5	$z = -2.05; p = 0.04$
Non-word	26	34.8	$z = -3.45; p < 0.001$
Mixed	26	34.8	$z = -3.4; p < 0.001$
Blend	28	31.78	$z = -2.1; p = 0.03$
Circumlocution	28	31.7	$z = -2.1; p = 0.03$
Unrelated	24	38.8	$z = -3.44; p < 0.001$

**Table 5.** Naming performance in healthy aging and patients with moderate Alzheimer disease and significant differences according to the nonparametric Mann-Whitney test

Naming performance	Normal aging ( <i>n</i> = 35), mean rank	Moderate Alzheimer ( <i>n</i> = 23), mean rank	Statistics and <i>p</i> value
Correct answers	41	12	$z = -6.5; p < 0.001$
Total errors	18	47	$z = -6.5; p < 0.001$
No response	19.7	44.9	$z = -5.58; p < 0.001$
Semantic	27.5	32.5	$z = -5; p < 0.001$
Non-word	24	37.8	$z = -4.48; p < 0.001$
Mixed	22.5	40.1	$z = -5.25; p < 0.001$
Blend	27	33.3	$z = -2.86; p = 0.004$
Circumlocution	21	42.4	$z = -5.9; p < 0.001$
Unrelated	22	40.9	$z = -5.42; p < 0.001$

**Table 6.** Naming performance in patients with mild Alzheimer disease and patients with moderate Alzheimer disease and significant differences according to the nonparametric Mann-Whitney test

Naming performance	Mild Alzheimer ( <i>n</i> = 23), mean rank	Moderate Alzheimer ( <i>n</i> = 23), mean rank	Statistics and <i>p</i> value
Correct answers	33.6	13.3	$z = -5.1; p < 0.001$
Total errors	13.5	33.6	$z = -5.1; p < 0.001$
No response	14.5	32.4	$z = -5.58; p < 0.001$
Semantic	15.78	32.5	$z = -4; p < 0.001$
Non-word	20.8	26.1	$z = -4.48; p = 0.02$
Mixed	20	27	$z = -2.04; p = 0.04$
Blend	22.5	24.5	$z = -7.69; p = 0.4$
Circumlocution	15.59	31.4	$z = -4.4; p < 0.001$
Unrelated	18.52	33.48	$z = -2.4; p = 0.006$

**Table 7.** Percentage of correct responses on the word-picture matching task based on type of errors

Type of errors	Normal aging	Mild Alzheimer	Moderate Alzheimer
No response	100%	98%	64.92%
Semantic	100%	100%	100%
Non-word		100%	98.25%
Formal		100%	100%
Perseveration		100%	100%
Mixed		100%	100%
Blend		100%	100%
Circumlocution		100%	95.77%
No remember		100%	100%
Unrelated		100%	63.16%
Visual	100%	100%	100%

elderly were significantly different from patients with moderate Alzheimer's, and there was also a significant difference between patients with mild Alzheimer's and patients with moderate Alzheimer's ( $p < 0.05$ ).

## Discussion

This study aimed to provide evidence to problems of naming and its nature in patients with Alzheimer's disease. The results of the study showed that anomia is one of the common problems of patients with Alzheimer's; in the moderate phase of disease, anomia develops as well. With progress of disease, number of incorrect responses increases. Naming errors in the initial phase of disease are different from the healthy elderly in terms of quantity and as the disease grows, the quality of errors is different as well.

Generally, based on the results around having significant differences in all three groups, there are differences between the healthy elderly and patients with mild and moderate Alzheimer's, and also between the patients with mild Alzheimer's and moderate Alzheimer's. The study in which classification was based on the disease severity shows differences between the healthy elderly and patients with Alzheimer's as the number and the nature of errors change as the disease develops [2, 22]. In the present study as it was noted earlier, in addition to number of errors, patterns of errors change through the development of disease as well. The cause of changes in patterns may be due to changes in fundamental causes of anomia in different phases of the disease. In the moderate phase of disease, the number of all type of errors increased. The increase in no response errors, semantic errors, non-word, unrelated, and mixed errors was significant.

Most errors made by the healthy elderly and patients with mild Alzheimer's were semantic errors. The errors in early stages of disease may be due to problems with lexical retrieval, but in late stages, degradation of concepts implies is the cause of these errors [22].

Systematically semantic errors do not represent semantic system damage; they may represent deficits in retrieving the phonological form of a word and conceptual knowledge access visually [12]. Based on the two-step interactive model when facing a concept, picture or object, first representative units of the target word semantic features are activated, then due to the connection between nodes and spreading activation, those nodes which have something in common with the target word are activated as well. Due to brain problems, the weight of semantic layer may decrease and the noise activity may increase; as a result,



semantic errors are made [16]. In addition, an increase in semantic errors shows a more severe deficit in lexical access in patients with moderate Alzheimer's.

The frequency of no response errors was high in patients with moderate Alzheimer's. In this type of error, there was no response from the person, which can be a sign of failure in lexical activation; in fact, when lexical retrieval is being done, related nodes to target word have more activity; then, this level of activity goes to the other layers through spreading activation. Although in no response status, semantic layer has not had enough activity and that cannot go through the other layers [23].

Circumlocution error increases with the development of disease as well. In this error, the person has access to semantic features related to the target picture, although the access to the phonological form of the target word is still a problem. However, this type of error can be considered as a compensatory function to naming problems [24]. It seems that an increase in this type of error in patients with moderate Alzheimer's is a sign of more difficult access to the phonological form of a word as the disease progresses.

In unrelated errors, the target word was substituted by another word which was away from the target word semantically and phonologically. In this case, due to network noise, target semantic layer does not have the suitable activity; therefore, the right lemma cannot be chosen, and the other semantic nodes which are away from the target word can reach the suitable level of activity and the unrelated word is chosen [25].

Patients with mild and moderate Alzheimer's made mixed errors, while healthy people did not make such error. In this type of error, another word which is semantically and phonologically close to the target word substitutes the target word, which shows problems in lexical access and spreading activation in lexical layers [25]. Differences between these errors in the healthy elderly and patients with mild Alzheimer's may represent the problems of most patients with Alzheimer's in lexical retrieval. Blend errors happened in all groups of Alzheimer's in which the response was a one-word response combining two synonyms.

Non-word errors can be due to noise in phonological layer in which unsuitable nodes are chosen instead of the suitable ones. On the other hand, decrease in phonological parameter causes inappropriate connection between phonological and semantic layers; as a result lexical layer is not able to activate suitable nodes [25]. In the moderate phase of disease, the percentage of these errors increases which makes the phonological access more difficult.

In case of conceptual knowledge or access to concept, the healthy elderly matched all pictures they had named incorrectly, which shows that access to concept in this group has no problem and it seems that their errors are probably due to having problem in lexical access.

Patients with mild Alzheimer's on the other hand could match fewer pictures they had trouble naming in comparison with the healthy elderly and this number was much less than the other groups in patients with moderate Alzheimer's. This result shows that in the moderate phase of disease, matching ability in patients decreases significantly.

Results of some studies showed that naming problems in the early phase of Alzheimer's disease may occur due to problems in access to phonological label of words while in more developed stages of disease, naming problems may occur due to damage in the semantic and processing system of the person [25]. According to the number and type of mentioned errors in this study and also decrease in matching ability, results of this study confirm this theory.

In the moderate phase of disease, a decrease in correct responses in picture matching assignment may be reflection of damage of conceptual knowledge in patients with Alzheimer's. It is not just problems of lexical access, in the moderate phase of disease, conceptual knowledge problems appear as well. It must be noted that existence of circumlocution error and semantic

error shows the existence of conceptual knowledge and concept access. It may be the same in case of non-word error too. In these errors, the phonological arrangement of lemma is not done correctly [25]. However, in some other types of errors, there is also the possibility of access to the semantic system; semantic access in these three types of errors is definite. Matching assignment was done in all types of errors in this study.

## Conclusion

Error analysis in the present study showed that naming function is different in the healthy elderly and patients with Alzheimer's in terms of quantity and quality. Error analysis showed that lexical access including access to lemma and access to phonological form of words has problems in these patients and the same experience happens to the healthy elderly. In the moderate phase of disease, not only phonological and semantic retrieval becomes more difficult, but conceptual knowledge changes as well. In the early phase of the disease, lexical access has problems, but with the development of the disease, problems in conceptual knowledge appear as well.

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## Statement of Ethics

This article was extracted from the Master's thesis entitled "Study of Frequency and types of errors in naming performance in healthy aging and patient with mild and moderate Alzheimer disease." The thesis has been reviewed and approved scientifically by the research council of Isfahan University of Medical Sciences (registration code: 395249), and the whole procedure was approved by the Ethics Committee of Isfahan University of Medical Sciences (ethics code: IR.MUI.REC.1395.3.249).

## Disclosure Statement

We declare no conflict of interest.

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