NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2020;57:9–14
https://doi.org/10.29399/npa.23521

# Investigation of the Processing of Noun and Verb Words with fMRI in Patients with Schizophrenia

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**ABSTRACT**

**Introduction:** Action naming is reported to be more damaged in patients with schizophrenia than object naming. Aim of this study is to understand the cortical mechanism underlying the negative symptoms seen in patients with schizophrenia such as inactivity, restricted behavioral repertoire, by using functional MRI (fMRI) to determine whether the action origin words have a different representation in the brain regions of patients with schizophrenia and healthy individuals. Our hypothesis is that restriction in the repertoire of movement and behavior and the failure of words of "action" than words of "object" are interrelated through the same cortical mechanisms. If this hypothesis is correct, the reason for not taking action in patients with schizophrenia may be improper definition of the action (verb).

**Methods:** fMRI study was conducted with 12 patients with schizophrenia and 12 healthy individuals. fMRI recording was performed after applying positive and negative syndrome (PANSS) scale, Calgary depression scale, hand preference scale to the participants. During the sessions, "lexical decision task" is applied by showing a total of 240 words (120 words – 60 verbs (words of action) and 60 nouns (words of object) – and 120 non-words) to the subjects.

**Results:** In fMRI findings, in the group main effect, which can also be expressed as the difference of the noun and verb words in the group of schizophrenia from the noun and verb words in the healthy control group, the activation of the anterior prefrontal cortex is found to be lower in patients with schizophrenia than in healthy individuals. When the brain areas which show the difference in verb words in schizophrenia group from both noun words in schizophrenia group and noun and verb words in healthy individuals are examined, inferior frontal gyrus pars triangularis (BA45) showed more activation in patients with schizophrenia than healthy individuals, but again for the same task, inferior frontal gyrus pars opercularis (BA44) and left primary sensory area showed less activation in patients with schizophrenia than healthy individuals. There is no difference between patients with schizophrenia and healthy volunteers in terms of correctly identified words and reaction time.

**Conclusion:** Considering the lack of difference between the groups in terms of number of correctly identified words and reaction time, and BA 44's role in recognition and imitation of action and being a part of the mirror neuron system, the significant inverse correlation between PANSS negative score and BA40 can be seen as an effort to compensate for BA44 inadequate activity through BA40.

**Keywords:** Language in schizophrenia, fMRI, lexical decision task

**Cite this article as:** Nazlı ŞB, Koçak OM, Kırkıcı B, Sevindik M, Kokurcan A. Investigation of the Processing of Noun and Verb Words with fMRI in Patients with Schizophrenia. Arch Neuropsychiatry 2020;57:9-14.

## INTRODUCTION

Schizophrenia is a chronic disorder that affects about 1% of the population, usually starts before the age of 25, is seen in all social classes, and impairs interpersonal and occupational functioning (1). It is a psychiatric disorder that causes disturbances in thought content and language and interferes with interpersonal interactions. Schizophrenia is sometimes called "language-related human-specific illness" or "logopathy" by some authors (2).

Studies indicate that there is a greater deterioration in the naming of action than that of the object in patients with schizophrenia in comparison to healthy individuals (3). However, the literature review shows that this difference has never been detected by fMRI studies. This issue indicates an important point in understanding cognitive characterization in schizophrenia and the representation of object and action names in the brain.

When the proper naming of actions (verb) and objects (noun) were compared in the studies, it was seen that the names of actions in patients with schizophrenia were considered more difficult than that of the objects (4, 5).

While in schizophrenia, linguistic problems are mostly involved in formal thought disorder, there are also symptoms such as difficulty in finding words and reduced expression related to negative symptoms. In addition

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**Received:** 01.12.2018, **Accepted:** 15.08.2019, **Available Online Date:** 28.11.2019

to the decreased quantity of speech in negative symptoms, there is also a reduction in behavioral repertoire and diversity and a general inactivity (3).

In this study, the aim is to establish a meaningful relationship between brain regions that differ in verbs and negative symptoms, especially inactivity and clinical symptom severity associated with narrowing of behavioral repertoire, in the schizophrenia group compared to the control group, to understand the cortical mechanisms behind the negative symptoms. The hypothesis is: Restrictions on movement and behavioral repertoire of the negative symptoms are likely to be linked with the same cortical mechanisms implicated in the failure of processing in verbs according to the nouns. If this hypothesis is correct, the reason for not taking action in patients with schizophrenia may be improper definition of the action (verb).

## MATERIALS AND METHODS

### Participants

Twelve patients diagnosed with schizophrenia who were treated at Kırıkkale University Faculty of Medicine and 12 healthy volunteers who had no previous or present psychopathology were included in the study. Informed consent of the patients and ethics committee approval are available.

### Inclusion Criteria

The inclusion criteria for patients with schizophrenia are to be between 18 and 50 years of age, to have at least secondary school education, to have been diagnosed with schizophrenia according to the DSM-5 diagnostic criteria, and to have signed the informed consent form. The inclusion criteria for the control group are to be between the ages of 18 and 50, to have signed the informed consent form, and to be healthy volunteers matched to the age group and education level by the patients with schizophrenia.

### Exclusion Criteria

For the patients with schizophrenia, the exclusion criteria are: presence of a psychiatric and neurological disorder other than schizophrenia, use of alcohol and substances, a medical condition that prevents the use of the MR device. For the control group, exclusion criteria are: any psychiatric, neurological or medical illness and a medical condition that prevents entry into the MR device.

Sociodemographic features of the subjects included in the study were recorded. Subsequently, positive and negative syndrome (PANSS) scale, Calgary depression scale, hand preference scale were applied to patients with schizophrenia. Likewise, the sociodemographic features of healthy individuals were recorded, followed by the hand preference scale. Both groups were then placed in the MR device, which lasted for approximately 45 minutes with preliminary preparation, and fMRI was performed.

### Scales Used in Study

### Sociodemographic Information

The sociodemographic information form is prepared by ourselves. The form includes questions such as age, gender, marital status, educational status. The previous and current status of the patients with schizophrenia and healthy individuals were assessed.

### Positive and Negative Syndrome (PANSS) Scale

PANSS, a 7-point semi-structured interview scale with 30 items, is a scale developed by Kay et al. and has three subscales under the titles "positive syndromes", "negative syndromes" and "general psychopathology" (6). The Turkish reliability and validity study of the scale was conducted by Kostakoğlu et al. As a result, the PANSS adaptation in Turkish also shows high internal consistency, construct validity and inter-scorer reliability (7).

### Calgary Depression Scale

To assess the level and severity of depressive symptoms in patients with schizophrenia, this scale is developed by Addington et al. in 1992, and is a scale consisting of 9 items of the quadruple Likert type and evaluated by the interviewer (8). Scale includes depressive mood, hopelessness, feeling of worthlessness, reference thoughts about guilt, pathological guilt, morning depression, early awakening, suicide and observed depression symptoms. Aydemir et al. conducted the Turkish validity and reliability study. In the Turkish version, the cut-off score for schizophrenia accompanied by depressive disorder was 11 (9).

### Hand Preference Scale

In this questionnaire, subjects are asked which hand they usually use when they are writing, drawing, throwing something, using a hammer, brushing their teeth, erasing with an eraser, using scissors, striking matches, stirring a tin of dye, using a spoon, using a screwdriver, opening a jar and using a fork without a knife. The Turkish reliability and validity study of the test, which was developed by Chapman and Chapman in 1987, was carried out by Nalçacı et al. (10). The Turkish reliability of the scale was r = 0.993 and the internal consistency Cronbach alpha value was 0.97. Each answer given as right hand must be given 1 point, each answer for both hands must be given 2 points, and each answer for left hand must be given 3 points. Scores range from 13 to 39 points. If right hand is the active hand, score is closer to 13 points, while left hand is the active hand, score is closer to 39 points.

### fMRI Experiment Design and Analysis of Data

For 12 patients with schizophrenia and 12 healthy individuals, T1 recording including 1 entire brain, an anatomical (structural) view, T2 images of 5 sessions each session taking about 5 minutes were done. A total of 240 words were shown to subjects during the sessions. At the beginning of the session recording, details of the setup are described to participants.

120 of the 240 words shown in total, are Turkish words, but the remaining 120 non-words are not. Sixty of these 120 meaningful words were chosen as nouns and 60 of them were verbs, 30 of 60 nouns were chosen as concrete words and 30 of them were abstract words. Attention has been paid to ensure that the periodicity and frequency of the use of nouns and verbs is equal with the help of statistics. At the same time, the number of letters between verbs and nouns as well as between words and non-words are equated with the help of statistics.

The subjects are asked to press the "navy blue" button under their hands if they think that word is a word used in Turkish and "yellow" button if they see a word that is not available in Turkish. For the words used during the lexical decision task; abstract, concrete and verb discrimination were made, and a questionnaire was prepared for the abstractness-concreteness values of the words and the words that were out of the average were removed.

The tasks were reflected on the screen inversely in the MR room with the help of a monitor, and the subjects were allowed to read the words with the aid of the mirror placed in the eye-line. The total of 5 sessions lasted approximately 45 minutes each with preliminary preparation.

MR scans were made on a 1.5 tesla MR device (Philips). FOV RL was 230 mm, AP was 230 mm, FH was 88 mm, Voxel size was RL 3.59 mm, AP was 3.59 mm, slice thickness was 4 mm, and recon voxel size was 3.59 mm. Act TR / TE was 4000/50 ms. EPI factor was 39. The ACQ matrix was M×P 64×64.

Prior to the acquisition of the activation signals, the fMRI data needs "pre-processing" operations such as image alignment and motion correction. The fMRI data of the subjects were analyzed with SPM 12 running on MATLAB program and the behavior data were analyzed with SPSS. After whole brain analysis was conducted on SPM 12, the contrast value of the voxel of the maximum activity of those regions that belongs to the task that significant activity has occurred, was taken for each individual. The reason is to look at the disease symptoms and severity of the regions that where showing significant activity.

## RESULTS

### Demographic and Clinical Features

A total of 24 subjects, 12 patients with schizophrenia and 12 healthy individuals, were included in the study. The mean age of the 24 subjects was 32 y (standard deviation (SD): 10.121 min-max: 19-50 y). There was no statistically significant difference between patients with schizophrenia and healthy individuals in terms of gender, education, marital status, occupation, additional medical illness, alcohol substance abuse (Table 1).

Individuals were clinically evaluated with PANSS positive, PANSS negative, PANSS general pyschopathology, PANSS total, Calgary depression scale and Hand preference scale. Significant difference was found in all applied tests except for hand preference scale. There was no significant difference in hand preference scale (sig 0.822). While the hand preference score for patients with schizophrenia is 14.250 (SD: 0.753), the hand preference score for healthy individuals is 14.333 (SD: 0.651) on average (Table 2 and Table 3).

According to ANOVA, the group main effect was not found in terms of the number of correctly identified words (F 1.118 = 2.475, P = 0.118). Word main effect was not detected (F 1.118 = 0.591, P = 0.444). In addition, significant group×word effect was not detected (F 1.118 = 0.323, p = 0.571).

In terms of reaction times, neither group effect (F 1.118 = 0.064, p = 0.801) nor word type effect (F 2.236 = 1.482, p = 0.229) or group×word type effect (p = 0.902) was found according to ANOVA.

### fMRI Findings

The group's main effect can also be expressed as the difference of correctly identified noun and verb words in schizophrenia group from the noun and verb words in healthy control group, right Brodmann (BA) 10 (anterior prefrontal cortex) activation was found to be lower in patients with schizophrenia than healthy individuals. In addition, in our study, left BA 40 and left BA 45 (inferior frontal gyrus pars triangularis) were significantly activated in patients with schizophrenia compared to healthy individuals when the brain areas examined, which show differences between verbs in patients with schizophrenia and, both nouns in patients with schizophrenia and nouns and verbs in healthy individuals; however, the left BA 44 (inferior frontal gyrus pars opercularis) and the left primer sensory field (BA 1) showed less activation for the same task in patients with schizophrenia than healthy individuals. Besides, the left primary sensory area of the brain, which distinguishes concrete nouns from all other word types in this group in patients with schizophrenia and from all the word types in healthy individuals, is more active in patients with schizophrenia. When the brain areas, which distinguish the abstract

**Table 1.** Numbers and distribution percentages of demographic data in individuals with schizophrenia and healthy individuals

| | Individuals with schizophrenia N=12 (%) | Healthy individuals N=12 (%) |
|---|---|---|
| Gender | | |
| Female | 5 (41.6) | 4 (33.3) |
| Male | 7 (58.3) | 8 (66.6) |
| Marital status | | |
| Single | 8 (66.6) | 7 (58.3) |
| Married | 4 (33.3) | 5 (41.6) |
| Education level | | |
| High School | 11 (91.6) | 12 (100) |
| University | 1 (8.3) | 0 (0) |
| Working status | | |
| Working | 7 (58.3) | 7 (58.3) |
| Not working | 5 (41.6) | 5 (41.6) |
| Physical illness | | |
| Present | 0 (0) | 0 (0) |
| Absent | 12 (100) | 12 (100) |
| Alcohol and substance abuse history | | |
| Present | 2 (16.6) | 0 (0) |
| Absent | 10 (83.3) | 12 (100) |
| Family's psychiatric disorder history | | |
| Present | 2 (16.6) | 0 (0) |
| Absent | 10 (83.3) | 12 (100) |

**Table 2.** Clinical scale scores and the differences between two groups

| | Individuals with schizophrenia | Healthy individuals |
|---|---|---|
| PANSS* positive | 11.416 (SD: 2.644) | 7 (SD: 0) |
| PANSS* negative | 19.666 (SD 3.601) | 7 (SD: 0) |
| PANSS* general psychopathology | 24.083 (SD: 3.579) | 16 (SD: 0) |
| PANSS* total | 55.166 (SD: 7.493) | 30 (SD: 0) |
| Calgary depression scale | 2.416 (SD: 2.574) | 0 (SD: 0) |

* PANSS, positive and negative syndrome scale.

**Table 3.** The number of correctly identified words of nouns and verbs (abstract and concrete word) in patients with schizophrenia and healthy individuals

| | Group | Mean | SD | Number |
|---|---|---|---|---|
| The number of correctly identified verb words | Schizophrenia | 55.5000 | 7.01297 | 12 |
| | Control | 57.7500 | 1.42223 | 12 |
| | Total | 56.6250 | 5.08033 | 24 |
| The number of correctly identified abstract noun words | Schizophrenia | 26.3333 | 5.78923 | 12 |
| | Control | 28.5833 | 1.31137 | 12 |
| | Total | 27.4583 | 4.26287 | 24 |
| The number of correctly identified concrete noun words | Schizophrenia | 26.9167 | 5.36755 | 12 |
| | Control | 28.7500 | 1.13818 | 12 |
| | Total | 27.8333 | 3.90837 | 24 |

**Table 4.** Group main effect

| Area | Brodmann area | Number of voxels in the cluster | F value | X Y Z | P(FWE)** corrected |
|---|---|---|---|---|---|
| Anterior prefrontal cortex | RIGHT BA* 10 | 56 | 48.76 | 43 46 10 | p<0.001 |

* BA, Brodmann area.
** FEW, family-wise error.

**Table 5.** The differences between verb words in patients with schizophrenia and, both noun words in patients with schizophrenia and noun and verb words in healthy individuals

| Area | Brodmann area | X Y Z | Number of voxels in the cluster | F value | P(FWE)** corrected |
|---|---|---|---|---|---|
| Parietal cortex | Left BA* 40 | -48 -21 18 | 30 | 54.85 | P<0.001 |
| Inferior frontal gyrus Pars operculais | Left BA* 44 | -44 7 6 | 96 | 54.60 | P<0.001 |
| Parietal cortex | Left primary sensory area (1) | -52 -18 46 | 83 | 48.15 | P<0.001 |
| Inferior frontal gyrus Pars triangularis | Left BA* 45 | -41 28 2 | 12 | 34.22 | P=0.002 |

* BA, Brodmann area.
** FEW, family-wise error.

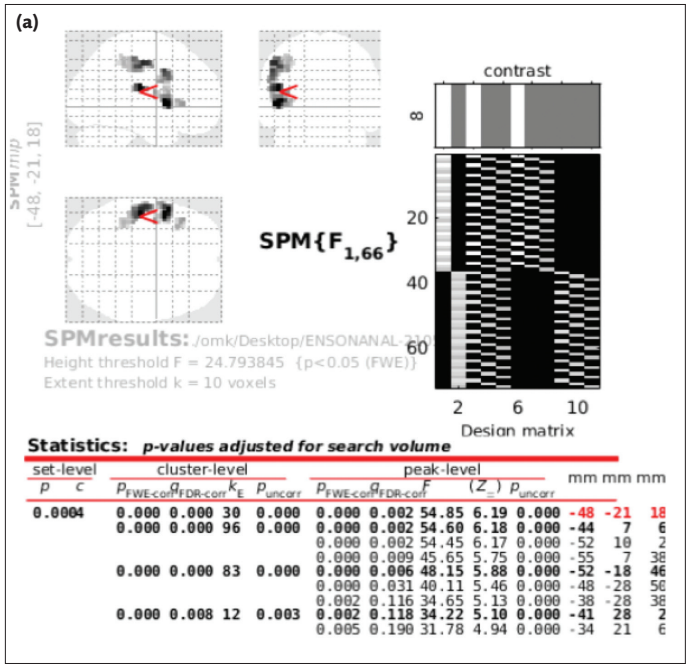
nouns from all other word types in the patients with schizophrenia and in healthy individuals, were examined, less activation was found in the patients with schizophrenia than in the healthy individuals in inferior frontal gyrus pars opercularis. The behavioral data show that both for the reaction time and the number of correctly identified words, no statistically significant difference was found between the patients with schizophrenia and the healthy individuals in terms of groups and word type (Table 4 and Table 5).

We found negative correlations between the activation of BA 40 area and PANSS total score (p=0.008, r=-0.723), PANSS negative score (p=0.046, r=-0.723), and PANSS general psychopathology score (p=0.025, r=-0.639), when we looked at the difference in the processing of the verbs from other nouns in patient with schizophrenia and from verbs and nouns in healthy individuals. There is no correlation between the same region and the PANSS positive scores (Fig. 1).

## DISCUSSION AND CONCLUSION

A role for rostral prefrontal cortex (BA10) has been proposed in multitasking, in particular, the selection and maintenance of higher order internal goals while other sub-goals are being performed. BA10 has also been implicated in the ability to infer someone else's feelings and thoughts, often referred to as theory of mind (11).

To detect cytoarchitectonic abnormalities in the Brodmann area 10 (BA10) of schizophrenic patients, Vogeley et al applied a newly modified



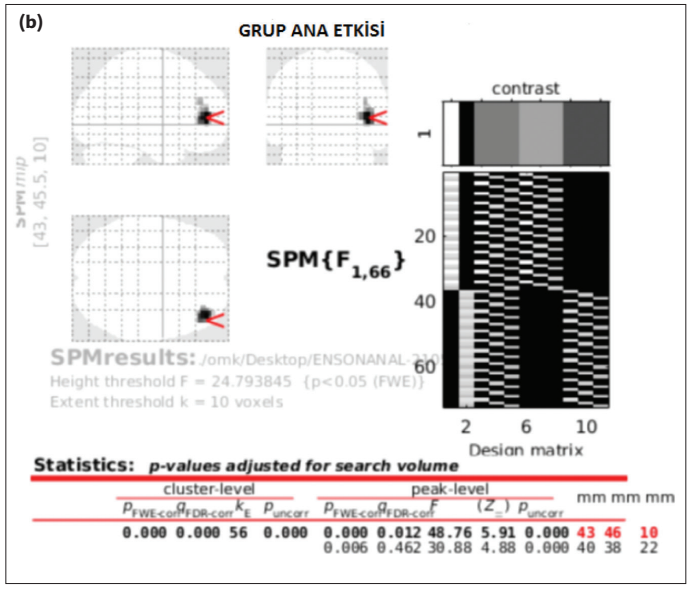




**Figure 1. a, b.** The brain areas that differs in verbs in patients with schizophrenia and, from both nouns in patients with schizophrenia and nouns and verbs in healthy individuals (a). Group main effect (b).

variant of the gray-level index (GLI) method as fully automated image analysis method providing cytoarchitectonic profiles of the whole cortex as a scanning tool (12). The relationship between BA 10 and schizophrenia has also been examined in our study.

In our study, in the group main effect, which can also be expressed as the difference of the nouns and verbs in the group of patients with schizophrenia from the nouns and verbs in healthy individuals, right Brodmann (BA) 10 activation was found to be significant.

BA 10 is the Brodmann area which has the largest volume in the anterior cortex. It is also known as the frontopolar prefrontal cortex (FPPFC), the rostrolateral prefrontal cortex (RLPFC), or the anterior prefrontal cortex. It is 14 $cm^3$ in volume and corresponds to 1.2 percent of total brain volume. Left BA 10 has been reported to be involved in integration with higher cognitive processes (13).

In our study, when the brain areas which show the difference in root words in schizophrenia group from both nouns in patients with schizophrenia and nouns and verbs in healthy individuals are examined; both in left BA 40 and left BA 45 (inferior frontal gyrus pars triangularis) excess activation have been shown in schizophrenia group in comparison to the healthy controls.

The lower part of BA 40, which is a part of the "parietal cortex" in the human brain, is the supramarginal gyrus. BA 40 is known to have a place in "visual word identification" (14). Unlike our work, some authors suggest that BA 40 is less active in patients with schizophrenia during assignments. For example, in Schultz's PET study in 2002, there was a negative correlation between the age of patients with schizophrenia and cerebral blood flow in BA 8 and BA 40 (15). Similar to our study, in an FMRI study conducted by Jiang et al. in 2015, working memory was examined with N-back task and an exaggerated response in the right dorsolateral prefrontal cortex (DLPFC) was observed in patients with schizophrenia compared to the control group. Similar results were shown in BA 46 and BA 40 (16).

Broca's area (BA 44 and BA 45) is located in the dominant hemisphere (usually on the left) in the frontal lobe. It is known as the sound production zone of the brain. It corresponds to "inferior frontal gyrus".

While inferior frontal gyrus pars triangularis receives more afferent connections from the prefrontal cortex, upper temporal gyrus, and upper temporal sulcus, inferior frontal gyrus pars opercularis receives afferent connections from the motor, proprioceptive and lower parietal regions (17). Recent studies have shown that pars triangularis (PTr) and pars opercularis (Pop), which correspond to 45 and 44 respectively, played different functional roles in language perception and action recognition/ understanding in the human (18, 19). Broca is an effective brain region both in semantic recall and in action understanding (mirror neuron). For a long time it was thought that Broca's area was not only taking role in language perception, but it is also reported to be important in language understanding (20).

When the brain areas which show the difference in verbs in schizophrenia group from both nouns in patients with schizophrenia and nouns and verbs in healthy individuals are examined in our study, the left inferior frontal gyrus pars opercularis and left primary sensory field showed less activation in patients with schizophrenia than healthy individuals.

This leads to the assumption that the Broca region (BA 44 and BA 45) contains mirror neurons (18, 19) and that the Broca region is no longer regarded as a pure language domain but as a region that associates action and language at the same time (20, 21).

An increase in BA 40 activity in patients with schizophrenia is found when compared to healthy individuals. Considering the role of BA 40 in "identification of visual information", especially when the activity increase is in verbs in patients with schizophrenia, a compensatory visualization effort may be taking place in the creation of mental representations of action. In support of this, activity in this region was found to show significant inverse correlation with PANSS negative score. That is, as the activity of this zone increases, negative symptom scores decrease. In verbs, parallel to BA 40, there is an increase in activation in BA 45, in patients with schizophrenia relative to the healthy individuals. However, BA 44 activity in patients with schizophrenia is lower than in healthy individuals. Considering that BA 44 is a part of the mirror neuron system and its role in recognizing and mimicking actions, it may be said that "BA is working more as a compensation", although there is little activation there.

**Ethics Committee Approval:** This study follows the guidelines of the declaration of Helsinki.

**Informed Consent:** Patients have informed consent.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - ŞBN, OMK; Design - ŞBN, OMK; Supervision - OMK, ŞBN; Resource - ŞBN; Materials - ŞBN; Data Collection and/ or Processing - ŞBN, OMK, BK; Analysis and/or Interpretation - ŞBN, OMK; Literature Search - MS, AK; Writing - ŞBN; Critical Reviews - OMK, BK.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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