A Longitudinal Functional Magnetic Resonance Imaging Study of Working Memory in Patients Following a Transient Ischemic Attack: A Preliminary Study

Wei Su^{1,2} · Jian Guo¹ · Yun Zhang³ · Jie Zhou¹ · Ning Chen¹ · Muke Zhou¹ · Rong Li⁴ · Huafu Chen⁴ · Li He¹

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Abstract In this study, we used functional magnetic resonance imaging (fMRI) to investigate longitudinal changes in brain activation during a verbal working memory (VWM) task performed by patients who had experienced a transient ischemic attack (TIA). Twenty-five first-ever TIA patients without visible lesions in conventional MRI and 25 healthy volunteers were enrolled. VWM task-related fMRI was conducted 1 week and 3 months post-TIA. The brain activity evoked by the task and changes over time were assessed. We found that, compared with controls, patients exhibited an increased activation in the bilateral inferior frontal gyrus (IFG), right dorsolateral prefrontal cortex (DLPFC), insula, inferior parietal lobe (IPL), and cerebellum during the task performed 1 week post-TIA. But only the right IFG still exhibited an increased activation at 3 months post-TIA. A direct comparison of fMRI data between 1 week and 3 months post-TIA showed greater activation in the bilateral middle temporal gyrus, right DLPFC, IPL, cerebellum, and left IFG in patients at 1 week post-TIA. We conclude that brain

activity patterns induced by a VWM task remain dynamic for a period of time after a TIA, despite the cessation of clinical symptoms. Normalization of the VWM activation pattern may be progressively achieved after transient episodes of ischemia in TIA patients.

Keywords Functional magnetic resonance imaging · Recovery · Transient ischemic attack · Verbal working memory

Introduction

A transient ischemic attack (TIA) is classically characterized as a sudden, temporary dysfunction of one artery in the brain that induces focal symptoms [1]. Although it is generally considered that focal neurological deficits due to a TIA recover within 24 h, several lines of evidence indicate that TIA patients may exhibit a prolonged cognitive decline [2–4]. In particular, impaired attention, executive function, and psychomotor speed have been reported in TIA patients [2]. However, the exact mechanism by which a TIA affects brain functions related to cognitive performance remains unclear. As attention, executive function, and psychomotor speed are critical for verbal working memory (VWM) processes [5], it is reasonable to believe that VWM tasks provide a useful model with which to study the association between cognition and the activation of brain function in TIA patients. However, to the best of our knowledge, the cerebral activity patterns associated with the performance of a VWM task by TIA patients have not yet been fully explored.

Functional magnetic resonance imaging (fMRI) plays an integral role in defining the neural substrates and

Wei Su and Jian Guo contributed equally to this work.

✉ Li He
heli2003new@126.com

- ¹ Department of Neurology, West China Hospital of Sichuan University, Chengdu 610041, China
- ² Department of Science and Technology, West China Hospital of Sichuan University, Chengdu 610041, China
- ³ Department of Neurology, Mianyang Central Hospital, Mianyang 621000, China
- ⁴ Key Laboratory for Neuroinformation of The Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610041, China

mechanisms associated with diseases that affect cognitive function. For example, assessment of blood flow and oxygen concentration by fMRI has been used to elucidate the activation status of encephalic regions while a participant is performing a cognitive task. In recent fMRI studies that investigated patients suffering from various diseases associated with attention-execution dysfunction, many valuable discoveries related to the neurophysiological mechanisms underlying their VWM defects were revealed [6, 7]. And especially, fMRI has already been used to study blood-oxygen level dependent (BOLD) signal changes in the cortico-cerebellar circuit during a VWM task completed by patients that had undergone a stroke [8]. In addition, as fMRI is a non-invasive technique, it has been sufficiently validated for use in longitudinal studies [9]. Several longitudinal fMRI investigations have been conducted to assess changes in brain activation associated with recovery after stroke [9, 10]. However, although stroke and TIA share a similar pathophysiology, longitudinal fMRI evidence regarding VWM after a TIA has not been studied.

In the present study, we used task fMRI to study longitudinal changes associated with VWM-related cerebral function in a group of patients recently affected by a TIA. The goals were to determine whether VWM-related brain activity is altered in TIA patients and whether the activity patterns vary with time. We evaluated the acute stage 1 week after a TIA, and the post-acute stage 3 months after a TIA. It is anticipated that these results will provide valuable insight into the neurological mechanisms that mediate the development of cognitive dysfunction in TIA patients.

Participants and Methods

Participants

Between April 2013 and January 2016, 25 right-handed patients experiencing their first TIA in the right hemisphere were recruited. For controls, 25 right-handed healthy individuals were also enrolled. The study protocol was approved by the Local Ethics Committee of the West China Hospital, Sichuan University, and written informed consent was given by each individual prior to participation in the study.

The pre-specified inclusion criteria were as follows: (1) patients with syndromes of focal neurological dysfunction ascribed to a vascular territory lasting less than 24 h; (2) symptoms had occurred less than a week before inclusion in the study; (3) ABCD² Score ≥ 3 ; and (4) without brain lesions on conventional MRI [e.g., fluid attenuated inversion recovery (FLAIR) images or T2-weighted images]. All patients in the TIA group were evaluated by two senior

stroke neurologists and were confirmed for enrollment based on a consensus achieved at clinical team meetings prior to the start of the study. Exclusion criteria included: (1) patients younger than 40 years or older than 65 years of age; (2) posterior circulation or left hemisphere localization; (3) recurrent TIA/stroke during a 3-month follow-up period; (4) symptoms related to a non-ischemic diagnosis, such as a psychiatric disorder, seizure, or migraine; and (5) patients with pre-existing cognitive impairment or psychiatric diseases prior to TIA. The controls were 25 healthy volunteers matched for age, sex, and years of education with no history of stroke/TIA or other neurological disorders. Assessments of clinical parameters were carried out according to the protocols described in our previous study [11]. Computed tomography perfusion imaging and magnetic resonance angiography were conducted to identify the affected vascular territory. All patients and controls were subjected to the Montreal Cognitive Assessment (MoCA) before their first scan to evaluate their general cognitive function.

Data Acquisition

This study was designed as a longitudinal observational study involving fMRI experiments performed 1 week and 3 months after each patient's TIA. Data collected for the two time points for the two groups are reported as TIA1 and TIA2 group data, and the control1 and control2 group data. Imaging was performed using a 3-Tesla Trio scanner (Siemens AG, Erlangen, Germany) with an 8-channel birdcage head coil. Foam padding and headphones were used to limit head motion and reduce scanner noise. An echo-planar sequence was used while the participants performed a VWM task [repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; matrix 64×64 ; field of view (FOV) = $24 \times 24 \text{ cm}^2$]. High-resolution structural imaging of the whole brain was performed using a T1-weighted sequence (TR = 1900 ms, TE = 2.28 ms, matrix 256×256 , FOV $24 \times 24 \text{ cm}^2$) coplanar to the fMRI scans to aid in registration of the scans to the standard Montreal Neurological Institute (MNI) brain, thereby allowing analysis of fMRI in standard space. T2-weighted and FLAIR images were also acquired to detect clinically silent lesions.

Task paradigm

Working memory performance was measured using an event-related fMRI n-back task under two conditions (0-back and 2-back). Stimuli for the n-back task were designed and presented on a computer using E-Prime software (Psychology Software Tools, Inc., 2002, Pittsburgh, PA). In the 0-back condition, participants had to

press a button with the right index finger whenever the number ‘‘1’’ was displayed. During the 2-back condition, they were asked to decide whether the current number matched the number displayed two trials before. Two runs of a block-designed *n*-back VWM task with blocks of 2-back conditions and 0-back conditions were performed during each fMRI session, as previously described [12] (Fig. 1). Each run contained three 32-s blocks of the 0-back condition alternated with three 32-s blocks of the 2-back condition. Each block consisted of a sequence of 16 trials, each displayed for 200 ms with an interstimulus interval of 1800 ms. Task performance was assessed by measuring accuracy rates and the mean reaction time.

Data Analysis

Demographic data and cognitive characteristics were analyzed using SPSS (version 15.0, IBM, Chicago, IL). Differences in these variables between each group were calculated using a two-sample *t*-test and Pearson’s χ^2 -test. For behavioral data, the main effects of group and time and their interaction were analyzed under the framework of ANOVA.

Anatomical data were processed to obtain brain volume from the 3D T1-weighted structural images using Freesurfer software (<http://surfer.nmr.mgh.harvard.edu>). The brain volume was then treated as an external regressor in the subsequent multiple regression analysis if there was a significant difference between groups. The fMRI data were pre-processed using SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). For each participant,

functional images were slice-time-corrected, realigned, normalized to the MNI template, and smoothed using an 8-mm full-width at half-maximum Gaussian kernel. Subsequently, statistical analysis using the general linear model with hemodynamic response function was performed. To obtain the brain activation patterns for each group, this general linear model was applied to smoothed, normalized scans from all participants, and contrast images for the 2-back > 0-back condition for each group were generated. Contrasts were then submitted to second-level analyses. First, two-sample *t*-tests with age and gender as covariates were used to compare the 2-back > 0-back contrast between the controls and patients at the 1-week and 3-month time points. Second, variables in demographic and cognitive characteristics with significant differences between groups were also used as confounding covariates in the statistical analyses. To explore if brain activity was altered by working memory after a TIA, changes in *n*-back-related activation at the 1-week and 3-month time points were compared using paired *t*-tests. The threshold was set at $P < 0.05$ [family-wise error (FWE) corrected for multiple comparisons], with a minimum cluster size of 10 contiguous voxels. In addition, Pearson correlation analyses were performed to explore the relationship between the activities of the brain areas with significant intergroup differences and the neuropsychological performance of the TIA patients.

Results

Demographic and Clinical Measures

The study population consisted of 50 participants (31 males) with a mean age of 51 ± 6.24 years. All participants were right-handed and had completed an average of 10.5 years of education. The demographic profile, risk factors, and clinical features of all participants are listed in Table 1. There were no significant differences in age, gender, education, and other vascular factors between the TIA and control groups. None of the participants were found to have intracranial arterial stenosis. However, more TIA patients suffered from carotid artery stenosis than individuals in the control group (15/25 *versus* 3/25, $P < 0.001$).

All TIA patients experienced acute onset of paralysis or numbness on the left side of the body after a TIA. The median duration of symptoms was 45 min (range, 10 min to 1.5 h). When the patients were classified according to ABCD² scores, 9 (36%) were categorized as having a low risk, 14 (56%) were at medium risk, and 2 (8%) were at high risk for recurrent stroke. All patients received secondary preventive treatment with aspirin (56%),

Fig. 1 Blocked-design of the *n*-back verbal working memory task [12].

Table 1 Baseline characteristics of participants.

	TIA (<i>n</i> = 25)	Controls (<i>n</i> = 25)	<i>P</i> -value
Age (years), mean (SD)	52.5 (4.88)	49.5 (7.14)	0.085
Sex, males (%)	15 (60)	16 (64)	0.771
Education (years), mean (SD)	10.36 (2.66)	10.84 (3.01)	0.552
Risk factors (%)			
Hypertension	9 (36)	6 (24)	0.355
Diabetes	3 (12)	1 (4)	0.297
Hyperlipidemia	9 (36)	8 (32)	0.765
Atrial fibrillation	3 (12)	0 (0)	0.074
Smoking	7 (28)	5 (20)	0.508
Carotid stenosis	15 (60)	3 (12)	< 0.001
1%–49%	8 (32)	3 (12)	0.088
50%–69%	6 (24)	0	0.009
> 70%	1 (4)	0	0.312
Clinical features (%)			
Motor symptoms	22 (88)		
Sensory symptoms	17 (68)		
ABCD ² score (%)			
Low (0 to 3)	9 (36)		
Moderate (4 to 5)	14 (56)		
High (6 to 7)	2 (8)		
MoCA	26 (2.48)	27.12 (1.36)	0.054

TIA, Transient ischemic attack; SD, standard deviation.

MoCA, Montreal Cognitive Assessment.

clopidogrel (32%), or warfarin (12%). Patients were closely monitored for recognized vascular risk factors after they were enrolled in the study.

Cognitive Tests and Behavioral Data

Although it was not significant, the TIA group tended to have poorer MoCA scores (26 ± 2.48 versus 27.12 ± 1.36 , $P = 0.054$) than the control group (Table 1). The behavioral data are summarized in Table 2. During fMRI scanning, both groups had similar accuracy rates and reaction times for the 0-back and 2-back VWM tasks. Furthermore, we found no evidence for a significant time or

time $\times$ group interaction for n-back ($n = 0$ or 2) accuracy rates or reaction time.

Task-Related Brain Activation

There were no significant differences in brain volume between the TIA and control groups (1399.18 ± 165.21 mL versus 1368.33 ± 147.01 mL, $P = 0.641$). So the brain volume was not included as a covariant in the subsequent study. The differences in brain activation for the 2-back > 0-back contrast between TIA patients and healthy controls at each time point are shown in Fig. 2. Patients in the TIA1 group exhibited greater

Table 2 Behavioral data of participants.

Time point	Behavioral data	TIAs (<i>n</i> = 25)	Controls (<i>n</i> = 25)	<i>P</i> -value
1 week	0-Back accuracy rate, mean (SD)	95.69 (1.24)	96.65 (1.77)	0.349
	0-Back reaction times, mean (SD)	664.67 (23.46)	645.63 (38.41)	0.428
	2-Back accuracy rate, mean (SD)	82.64 (6.31)	85.45 (5.28)	0.06
	2-Back reaction times, mean (SD)	889.27 (25.83)	835.45 (36.93)	0.065
3 months	0-Back accuracy rate, mean (SD)	94.97 (1.19)	96.95(2.08)	0.097
	0-Back reaction times, mean (SD)	689.94 (32.51)	655.11(30.6)	0.071
	2-Back accuracy rate, mean (SD)	81.48 (6.77)	84.95(2.39)	0.074
	2-Back reaction times, mean (SD)	901.36 (27.02)	868.57(33.54)	0.192

Fig. 2 Group activation maps illustrating the contrasts between patients and controls (2-back *versus* 0-back in patients > 2-back *versus* 0-back in controls) at one week (A) and three months (B) after TIA ($P < 0.05$, FWE corrected, cluster > 20 voxels). Compared with controls, patients exhibited an increased activation in the bilateral

IFG, right DLPFC, insula, IPL and cerebellum during the task performed 1 week after the TIA (A), and in the right IFG at 3 months after the TIA (B). Cbl, cerebellum; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; INS, insula; IPL, inferior parietal lobe.

activity in the bilateral inferior frontal gyrus (IFG), right dorsolateral prefrontal cortex (DLPFC), insula, inferior parietal lobe (IPL), and cerebellum than controls ($P < 0.05$, FWE corrected; Fig. 2A, Table 3). Patients in the TIA2 group exhibited greater activity in the right IFG than the control group ($P < 0.05$, FWE corrected; Fig. 2B, Table 3). None of the other areas exhibited significant decreases in activity compared with the controls. As the degree of carotid stenosis and MoCA differed or were marginally different between groups, they were also used

as confounding covariates in the statistical analyses. We found that the addition of these two covariates to the analyses did not change the results.

When the parameters for the 0-back > baseline and 2-back > baseline contrasts were extracted from the right IFG, the enhanced activity was attributable to a marked increase in the BOLD signal during the 2-back condition in TIA patients at both time points assayed ($P < 0.001$ and $P = 0.046$) (Fig. 3). In contrast, there was no significant difference in the BOLD signals for the 0-back condition

Table 3 Functional magnetic resonance imaging signal change differences between groups during the verbal working memory task^a.

Brain areas	Coordinates (MNI)			Voxel size	Z value ^b	T value ^b	P-value
	X	Y	Z				
TIA1 > Control1							
R Dorsolateral prefrontal cortex	56	28	27	42	5.71	6.22	0.023
R Inferior frontal gyrus	36	3	27	20	4.85	5.08	0.048
R Insula	33	22	12	83	5.04	5.33	0.037
R Inferior parietal lobe	42	−39	33	39	5.83	6.39	0.021
R Cerebellum	15	−41	−30	104	5.15	5.46	0.036
L Inferior frontal gyrus	−37	4	30	59	5.33	5.7	0.034
TIA2 > Control2							
R Inferior frontal gyrus	37	6	30	21	5.34	5.71	0.034
TIA1 > TIA2							
R Dorsolateral prefrontal cortex	39	27	39	205	5.02	5.37	0.032
R Middle temporal gyrus	63	−27	−6	134	5.86	6.77	0.019
R Inferior parietal lobe	42	−48	60	46	5.07	5.42	0.026
R Cerebellum	18	−54	−27	64	5	5.33	0.039
L Inferior frontal gyrus	−45	−21	−3	63	4.88	5.18	0.045
L Middle temporal gyrus	−63	−36	−12	133	5.43	5.9	0.024

MNI, Montreal Neurological Institute

^a2-back WM > 0-back task contrast.

^bMaximum voxel-wise *t*-value within the cluster of interest.

Fig. 3 Higher working memory-related activation (2-back task) in the right inferior frontal gyrus (IFG) in patients than controls at one week (A) and three months (B) after TIA. The patients with TIA

exhibited significant over-activation of the IFG during the 2-back condition, but not during the 0-back condition, at both 1 week and 3 months.

between the two groups ($P = 0.139$ and $P = 0.098$). In addition, the TIA1 group exhibited greater activity in the IFG during the 2-back condition than the TIA2 group ($P < 0.001$).

The time-specific brain activity of patients with TIA was also investigated. The BOLD signals recorded from the TIA1 and TIA2 group were compared, and the TIA1 group showed higher activation during the 2-back > 0-back contrast in the bilateral middle temporal gyrus (MTG), right DLPFC, IPL, cerebellum, and left IFG than the TIA2 group (Fig. 4, Table 3). No other areas exhibited significantly lower cerebral activation. No significant correlations between these brain areas and the neuropsychological performance of the TIA patients were found. No dynamic changes of brain activation from baseline to 3 months were found in the control group.

Discussion

In this longitudinal study, brain activity in response to a VWM challenge was investigated at two time points in healthy controls and patients who had experienced a TIA. At the first time point (1 week after TIA), patients and controls performed similarly in the VWM task. However, the TIA patients exhibited significant over-activation of multiple brain areas during the task. At the second time point (3 months after TIA), clearly less task-related brain activity was recruited in patients, and only the IFG still exhibited an increase in activity during the VWM task. These results demonstrate that VWM-related functional activation patterns can vary following transient episodes of ischemia, and compromise of brain function due to a TIA may persist longer than the clinical symptoms associated with the attack.

Compared with the controls, TIA patients showed significantly greater brain activity in the bilateral IFG,

Fig. 4 Differences in brain activation of 2-back > 0-back contrast between the TIA1 group (1 week after a TIA) and the TIA2 group (3 months after a TIA). Compared with the TIA2 group, the TIA1 group showed higher brain activation during the 2-back > 0-back

contrast in the bilateral MTG, right DLPFC, IPL, cerebellum, and left IFG. Cbll, cerebellum; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; MTG, middle temporal gyrus.

right DLPFC, insula, IPL, and cerebellum 1 week after the TIA. All of these brain regions are essential for VWM function [13], especially the frontal and parietal lobes are universally considered to be the most important areas associated with VWM [14]. In previous studies, the IFG, DLPFC, and insula have been implicated in numerous cognitive functions that are relevant to the n-back task, including manipulation of information, reorganization and control of VWM, and increased task performance due to enhanced memory formation and reduced overall cognitive load which help with the structuring and categorizing of information [15–18]. Moreover, the IPL is generally considered to function as a more superior attentional modulator of VWM processes, shifting focal attention to related subordinate networks [19]. Cerebellum activation, however, is considered to be part of the cerebro-cerebellar circuit, which is hypothesized to provide the topographic functional organization of VWM [20].

The reason why these cerebral regions are over-activated remains unknown. It has been shown that stroke can lead to abnormal VWM [21]. One study using VWM task-related fMRI showed that brain activity in the cortico-cerebellar circuit increases after stroke [8]. The results of the present study further demonstrated that even without a permanent infarction, a TIA can induce lasting changes in brain activation that are manifested during a VWM task. These results are also consistent with those of Koerner and Edwards, who have shown that changes in cerebral activation can be sustained for a period of time after a TIA [22, 23].

Furthermore, direct comparison of brain activation exhibited during the acute and post-acute stages of a TIA

revealed that the IFG, cerebellum, DLPFC, and IPL were extensively activated during the acute phase. As these regions are the main components of the VWM circuit [13], these data indicate that TIA patients have a reduced capacity for maintaining normal VWM performance and thus undergo functional compensation to complete a VWM-related task. In addition, significantly less task-related brain activity was recruited 3 months after a TIA, which may reflect a normalization of cerebral function with recovery from a TIA.

When the acute phase was compared with the post-acute stage, the former was also associated with an over-activation of the bilateral MTG. Episodic and semantic memory have been linked to the temporal gyrus-related network [24]. Although it is not common and remains controversial, temporal activation has been detected in healthy individuals during a VWM task [25, 26]. Therefore, the results of the present study suggest that during a VWM task, TIA patients may recruit additional portions of the temporal gyrus-related network in order to maintain the level of performance that is needed for the task [27].

Another finding from the present study was that TIA patients exhibited significant over-activation of the IFG during the 2-back condition, but not during the 0-back condition, at both the 1-week and 3-month time points. These results are consistent with the report that an alteration in frontal lobe function is one of the earliest signs of vascular-related brain dysfunction after cerebral ischemia [28]. The IFG has extensive connectivity to other regions of the brain and is particularly sensitive to ischemic injury [29]. In stroke patients, frontal lobe dysfunction is a key factor in the cognitive impairment [30]. Recent

research on TIA has also shown that frontal lobe dysfunction is an early sign of transient ischemic effects on cognitive function [31]. The over-activation of the IFG in TIA patients in the present study may indirectly support the above view. Considering the fact that there was no significant defect in VWM performance in the patient groups, we further infer that the application of fMRI may detect vascular-related changes in frontal lobe function at the early stage of the disease, before VWM performance is substantially impaired. In addition, previous studies of stroke patients have found that the IFG plays an important role in the recovery of post-stroke language function [32], compromised language function being closely associated with limited VWM function [33]. Therefore, the activation of the IFG during the VWM task possibly reflects a reorganization of brain function after TIA, and this reorganization may be similar to that found after stroke. In addition, although the cases included in this study only involved right-sided TIAs, the IFG was activated bilaterally 1 week after the TIA, consistent with the report that VWM is mediated by both hemispheres [34].

Unexpectedly, no significant impairment of n-back performance was found in the patients examined. There are two possible reasons for this result. First, only comparatively young patients were recruited for this study, and previous studies have demonstrated that younger patients perform better on VWM tasks than older patients [35]. Second, most of the participants in this study did not have an extensive disease history, and patients with recurrent TIAs were excluded. Thus, functional alteration may not have been sufficiently explored using the traditional psychological scales employed in the present study. This reason is also consistent with the hypothesis that an extended pre-symptomatic period exists during the development of cognitive impairment after an ischemic attack [36].

To our knowledge, this is the first study to describe abnormal brain activity in TIA patients during a VWM task. Because TIAs can be heterogeneous, we only included patients who suffered a TIA in the same hemisphere and without visible infarction according to conventional MRI. Thus, the heterogeneity of the patient group was minimized. In addition, only patients with right-sided TIAs were examined; because all of these patients were right-handed, a diagnosis of left-sided TIAs may be interfered if the patients only had the clinical symptoms of speech disorder.

There were a number of limitations in this study. First, due to the small sample size, patients were not further stratified according to etiology. Second, although task-related brain activity in the patient group was clearly less recruited at 3 months, it remains unclear if and when brain activity returns to normal after a TIA. Hence, further

investigations of the transient effects of ischemia on brain activity, as well as the timeline of these effects, are necessary. Third, as a preliminary study, we failed to demonstrate correlations between the brain regions activated and the neuropsychological performance of the TIA patients. Further research with larger sample sizes and using more complex analysis such as psychophysiological interaction analysis is needed to explore such correlations.

Our results suggest that transient episodes of ischemia lead to changes in brain activation during VWM-related tasks. Nevertheless, these task-related activation patterns tend to normalize over time after the TIA. These findings provide additional insight into the neurobiological consequences of a TIA.

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Compliance with Ethical Standards

Conflict of interest All authors claim that there are no conflicts of interest.

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