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Detection of cognitive impairment in patients with obstructive sleep apnea hypopnea syndrome using mismatch negativity☆

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Abstract
In this experiment, 97 patients with obstructive sleep apnea hypopnea syndrome were divided into three groups (mild, moderate, severe) according to minimum oxygen saturation, and 35 healthy subjects were examined as controls. Cognitive function was determined using the mismatch negativity paradigm and the Montreal Cognitive Assessment. The results revealed that as the disease worsened, the mismatch negativity latency was gradually extended, and the amplitude gradually declined in patients with obstructive sleep apnea hypopnea syndrome. Importantly, mismatch negativity latency in severe patients with a persistent time of minimum oxygen saturation < 60 seconds was significantly shorter than that with a persistent time of minimum oxygen saturation > 60 seconds. Correlation analysis revealed a negative correlation between minimum oxygen saturation latency and Montreal Cognitive Assessment scores. These findings indicate that intermittent night-time hypoxemia affects mismatch negativity waveforms and Montreal Cognitive Assessment scores. As indicators for detecting the cognitive functional status of obstructive sleep apnea hypopnea syndrome patients, the sensitivity of mismatch negativity is 82.93%, the specificity is 73.33%, the accuracy rate is 81.52%, the positive predictive value is 85.00%, the negative predictive value is 70.21%, the positive likelihood ratio is 3, and the negative likelihood ratio is 0.23. These results indicate that mismatch negativity can be used as an effective tool for diagnosis of cognitive dysfunction in obstructive sleep apnea hypopnea syndrome patients.

Key Words
obstructive sleep apnea hypopnea syndrome; mismatch negativity; cognitive function; Montreal Cognitive Assessment; latency; diagnosis

Research Highlights
(1) Intermittent night-time hypoxemia is associated with abnormal mismatch negativity waveforms and Montreal Cognitive Assessment scores. (2) Mismatch negativity can be used as an effective tool for diagnosis of cognitive dysfunction in obstructive sleep apnea hypopnea syndrome patients.

Abbreviations
MoCA, Montreal Cognitive Assessment; ERPs, event-related potentials

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INTRODUCTION

Mismatch negativity is a change-specific component of auditory event-related potentials elicited by a deviant stimulus occurring in a sequence of repetitive stimuli. Mismatch negativity is thought to arise from the cortex, and is closely linked to perception[1-2]. The peaks of mismatch negativity appear at 150–250 ms from change onset, with this peak latency shortening with increasing magnitude of stimulus change. This component is thought to represent the automatic detection of acoustic changes and the initiation of an attentional switch. The mismatch negativity can be used to increase understanding of the neural processes underlying central auditory perception, and the different forms of auditory sensory memory[3]. Because mismatch negativity can be elicited even in the absence of attention, subjects do not need to actively participate. As such, it can reflect sensory memory function in the brain, and the ability of automatic processing of sensory information more objectively, meaning it can be used as an effective tool to evaluate cognitive function[4]. In recent years, mismatch negativity has been examined in a large number of different clinical conditions and used for auxiliary diagnosis of neurological diseases, psychological and mental disorders[5-6].

Obstructive sleep apnea hypopnea syndrome is characterized by repeated episodes of complete or partial cessation of breathing during sleep, associated with intermittent hypoxemia and fragmented sleep, which are significant nocturnal consequences of the disorder[7]. Many studies have reported a wide range of neurocognitive impairments in obstructive sleep apnea hypopnea syndrome patients, including selective and sustained attention[8-9], information processing speed[10], short-term memory including working memory, and executive functioning[11-13]. It has been proposed that vigilance and attentional deficits play a pivotal role in all aspects of the cognitive deficits noted in obstructive sleep apnea hypopnea syndrome[14-15]. Event-related potentials (ERPs) have been previously used to assess cognitive deficits in obstructive sleep apnea hypopnea syndrome patients, providing objective markers of cortical information processing[16]. ERPs are sensitive to the state of arousal, attention and vigilance[17] as well as cognitive deficits in many neurological conditions, and sleep deprivation/fragmentation[18]. The main ERP components associated with attention and information processing during an Oddball paradigm task[19] are the P_{3a}, P_{300} and mismatch negativity. Some studies have reported that obstructive sleep apnea hypopnea syndrome patients exhibit sustained and delayed P_{300} and P_3 latencies and a reduction in P_3 amplitude[8, 20-22], indicating that ERP responses may help identify cognitive dysfunction. However, these tests all used paradigms requiring attention, and the P_{300} is the most commonly used ERP component. In addition, most of these studies examined severe obstructive sleep apnea hypopnea syndrome patients only. Mismatch negativity is one of the auditory ERP components that can be elicited by passive auditory patterns, fewer studies have reported mismatch negativity changes in obstructive sleep apnea hypopnea syndrome patients with various degrees of pathology.

It is increasingly recognized that the neurocognitive deficits experienced by obstructive sleep apnea hypopnea syndrome patients are largely mild cognitive impairments, which had been confirmed by some neuropsychological tests, such as the Mini-Mental State Examination which is currently the most widely used tool. However, some studies have revealed that this measure is inadequate for detecting some neurocognitive deficits including mild cognitive impairment, and primarily test memory and language acquisition abilities[23]. Other familiar tests using aspects of the Wechsler test, mostly measure attention/memory function in cognitive impairment[24]. The Montreal Cognitive Assessment (MoCA) is a convenient, stand-alone cognitive assessment instrument that covers various important domains of neurocognitive functions and can be quickly administered to patients[25]. In the present study, we used this scale to screen cognitive function in obstructive sleep apnea hypopnea syndrome patients, and to examine the correlations between MoCA scores and mismatch negativity changes. This study was motivated by two key research questions: What are the characteristics of mismatch negativity in patients with obstructive sleep apnea hypopnea syndrome? What are the relationships between neuropsychological test scores and mismatch negativity changes? We utilized mismatch negativity as a measure of cognitive impairment in various pathological degrees of obstructive sleep apnea hypopnea syndrome patients according to their different levels of hypoxemia, and compared the data with MoCA test results to examine their correlation. In addition, we tested the diagnostic value of mismatch negativity, to identify and develop treatment for this impairment.

RESULTS

Quantitative analysis of subjects

According to their minimal blood oxygen saturation (minimum SaO_2) level, 97 obstructive sleep apnea hypopnea syndrome patients were included in this study, divided into three groups: Mild (85% ≤ minimum SaO_2 ≤ 90%; n = 30), moderate (65% ≤ minimum SaO_2 < 85%; n = 32) and severe (minimum SaO_2 < 65%; n = 35). In addition, 35 healthy adults were included as the control

group. All subjects were involved in the final analysis.

Demographic information

The illness history of obstructive sleep apnea hypopnea syndrome patients ranged from 5–6 years. All patients and controls were matched by age, gender and educational level (years of education ≥ 12, above high-school education), with no significant difference between the two groups ($P > 0.05$). All subjects exhibited normal hearing (testing frequency of pure tone test and acoustic immittance were normal). However, obstructive sleep apnea hypopnea syndrome patients exhibited significantly greater body mass index and higher daytime sleepiness than control subjects ($P < 0.05$; Table 1).

Table 1 Demographic and clinical characteristics of the subjects

Item	Obstructive sleep apnea hypopnea syndrome patients group			Control group (n = 35)
	Mild (n = 30)	Moderate (n = 32)	Severe (n = 35)	
Gender (n, male/female)	13/17	14/18	17/18	20/15
Age (year)	43.5±7.8	45.1±4.3	44.7±3.1	44.2±6.4
Body mass index (kg/m^2)	25.2±4.5[a]	28.7±3.9[a]	29.4±3.5[a]	22.4±2.3
Pathogenesis (year)	5.2±2.1	4.9±1.6	5.7±1.8	–
Educational level (year)	12.4±2.9	12.1±3.3	12.5±3.2	12.8±2.9
Daytime sleepiness (n)	20[a]	29[a]	33[a]	6

Data for age, body mass index, pathogenesis and educational level are presented as mean ± SD. [a]$P < 0.05$, *vs*. control group (one-way analysis of variance). Gender and daytime sleepiness were compared using the chi-square test.

Mismatch negativity change of obstructive sleep apnea hypopnea syndrome patients

Mismatch negativity latency prolonged and amplitude decreased as disease severity aggravated. The difference in mismatch negativity latency between mild, moderate to severe obstructive sleep apnea hypopnea syndrome patients and controls were statistically significant ($P < 0.05$). Although we found no significant differences in mismatch negativity amplitude ($P > 0.05$), the amplitude in the severe group appeared to be lower than that in other groups (Table 2).

According to the minimum persistent time of SaO_2, the severe patients group was further divided into two subgroups: minimum SaO_2 time < 60 seconds (n = 11) and > 60 seconds (n = 24), the distribution of mismatch negativity latency and amplitude are displayed in Table 3. The difference in mismatch negativity latency was statistically significant ($P < 0.01$), but there was no difference in mismatch negativity amplitude ($P > 0.05$).

Table 2 Comparison of mismatch negativity latency (ms) and amplitude (μV) in mild, moderate, severe patients with obstructive sleep apnea hypopnea syndrome and control groups

Group	n	Latency	Amplitude
Mild patients	30	164.51±11.22[a]	3.69±0.51
Moderate patients	32	186.69±9.54[a]	3.44±1.35
Severe patients	35	223.12±13.36[a]	3.19±1.44
Control	35	151.27±14.07	4.04±0.85

Data are presented as mean ± SD. [a]$P < 0.05$, *vs*. control group (one-way analysis of variance).

Table 3 Effect of minimum oxygen saturation persistent time on mismatch negativity in patients with severe obstructive sleep apnea hypopnea syndrome

Minimum SaO_2 time	n	Latency (ms)	Amplitude (μV)
< 60 seconds	11	214.0±13.7	3.2±2.8
> 60 seconds	24	224.6±16.7[a]	2.9±2.6

Data were presented as mean ± SD. [a]$P < 0.01$, *vs*. minimum SaO_2 time < 60 seconds group (one-sample t-test).

MoCA scores and correlations with mismatch negativity

Total MoCA scores decreased progressively as the disease severity aggravated, with significant differences between the mild, moderate and severe obstructive sleep apnea hypopnea syndrome patients and the control group ($P < 0.05$). The subdomain scores revealed a significant reduction in aspects of memory/delayed recall, visuospatial and executive function and attention in moderate-to-severe obstructive sleep apnea hypopnea syndrome patients compared with mild patients and the control group ($P < 0.01$; Table 4).

Table 4 Montreal Cognitive Assessment (MoCA) scores and subdomain scores among groups

Item	Obstructive sleep apnea hypopnea syndrome patients group			Control group (n = 35)
	Mild (n = 30)	Moderate (n = 32)	Severe (n = 35)	
MoCA scores	26.1±2.3[a]	24.7±2.7[a]	22.2±3.0[a]	27.4±2.5
MoCA subdomain scores				
Visuospatial & executive	4.5±0.7	4.4±0.7[ab]	4.2±0.6[ab]	4.7±0.6
Naming	2.9±0.3	2.9±0.3	2.8±0.3	2.9±0.5
Memory & delayed recall	3.3±1.3	3.2±1.5[bc]	3.0±1.3[bc]	3.5±1.0
Attention	5.6±0.9	5.4±0.9[bc]	5.3±0.7[bc]	5.6±0.7
Language	2.6±0.7	2.5±0.7	2.5±0.8	2.7±0.7
Abstraction	1.8±0.5	1.8±0.5	1.7±0.5	1.8±0.5
Orientation	5.9±0.3	5.9±0.3	5.9±0.2	6.0±0.4

Data are presented as mean ± SD. [a]$P < 0.05$, [b]$P < 0.01$, *vs*. control group; [c]$P < 0.01$, *vs*. mild group (one-way analysis of variance).

As mismatch negativity latency prolonged, the MoCA scores progressively decreased. Linear regression analysis revealed a statistically significant correlation between mismatch negativity latency and MoCA scores, with a Pearson correlation coefficient $r = -0.791$, $P < 0.01$ (Figure 1).

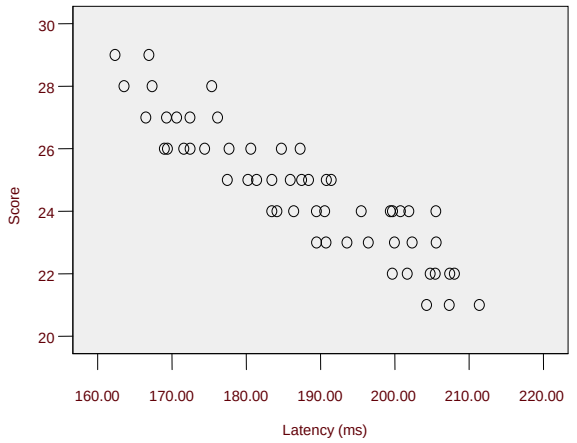

Figure 1 Mismatch negativity latency was negatively correlated with Montreal Cognitive Assessment scores ($r = -0.791$, $P < 0.01$).

The diagnostic efficacy of mismatch negativity in obstructive sleep apnea hypopnea syndrome patients

The prevalence rates of cognitive impairment in obstructive sleep apnea hypopnea syndrome patients tested using mismatch negativity and MoCA were 73.99% and 76.54%, respectively, and there was no statistical significant difference between them ($P > 0.05$). The diagnostic accuracy rate of mismatch negativity for mild cognitive impairment was 81.52%, the sensitivity was 82.93%, specificity was 73.33%, positive predictive value was 85.00%, negative predictive value was 70.21%, positive likelihood ratio was 3, and the negative likelihood ratio was 0.23.

DISCUSSION

Obstructive sleep apnea hypopnea syndrome patients with mild cognitive impairment commonly exhibit excessive daytime sleepiness and hypoxemia induced by nocturnal sleep-disordered breathing and apnea episodes[26]. These symptoms have been represented in several ways, most commonly in terms of attention and memory processing. A previous study reported that chronic nocturnal intermittent hypoxemia during sleep resulted in dysfunction of frontal executive cortex, which is particularly vulnerable to hypoxemia, and is proposed to constitute the pathological basis of memory impairment in obstructive sleep apnea hypopnea syndrome patients[13]. This effect may operate through the forehead and rear head area, generating electrophysiological activity patterns that lead to ERP abnormalities[27].

One of the distributions of mismatch negativity is a predominantly right-hemispheric frontal area, particularly the portion correlated to memory and linked to the hippocampal gyrus, generating a frontal mismatch negativity subcomponent[1, 28-29]. In non-note conditions, the maximal mismatch negativity is localized in the fronto-central region, which functions as an association area of sensory integration[30]. Mismatch negativity is thought to be generated by automatic detection and comparison processing of repetitive and regular sequences by auditory cortex, regardless of attention[3]. This characteristic enables mismatch negativity to be used for measuring patients that are typically difficult to study. For example, Fischer *et al* [31] reported that a patient's own name, presented as a deviant stimulus, elicited mismatch negativity in comatose patients.

The current study revealed that mismatch negativity latency significantly differed between obstructive sleep apnea hypopnea syndrome patients and the control group; as hypoxemia levels aggravated, the mismatch negativity latency prolonged progressively. Mismatch negativity latency is thought to reflect changes in stimulus attribution[30] and stimulus classification/detection processing speed, suggesting that the obstructive sleep apnea hypopnea syndrome patients in the current study may have exhibited impaired attention and automatic information processing. Obstructive sleep apnea hypopnea syndrome patients often suffer from sleep deprivation, particularly during the rapid eye movement sleep period, frequent arousal, and oxygen desaturation. These symptoms can be caused by respiratory and structural sleep disturbance, leading to extensive damage of the cerebral cortex, which is sensitive to hypoxemia. These findings suggest that hypoxemia is likely to be a significant factor in mismatch negativity latency abnormalities. Mismatch negativity amplitude is known to reflect changes of stimulus degree[30], and by the wakefulness state of the cerebral cortex, meaning that it is a relatively unstable measure. Although the test groups exhibited no statistically significant difference in amplitude, there was a trend towards an amplitude decrease as disease severity increased, especially in the severe group. The severe patients were likely to have suffered more severe hypoxemia, and the cortex typically becomes inhibited in response to the number and excitation of affected neurons.

It should be noted that the minimum persistent SaO_2 time in the severe group ranged from 2 seconds to 150 seconds. We set a minimum persistent SaO_2 time of 60 seconds as a cut-off point. Severe patients were then divided into two subgroups: minimum SaO_2 time <

60 seconds and > 60 seconds, the difference between the two groups was statistically significant. These results are likely due to the same severity of disease, but different persistent minimum SaO_2 times may result in different levels and areas of injury in the cerebral cortex. This result is consistent with previous research regarding the percentage of sleep time with SaO_2 below 90%[26]. Although the Apnea Hypopnea Index is more frequently applied as a measure of the severity of obstructive sleep apnea hypopnea syndrome patients, patients with the same Apnea Hypopnea Index score, their nocturnal hypoventilation and hypoxemia level and its persistent time are not uniform, and the degree of sleep structure disturbance is not necessarily the same. Thus, the Apnea Hypopnea Index is unable to distinguish the role of pathogenetic effects of time and the damage of cortex by long-term hypoxemia. Further studies have revealed that cognitive impairment was related to hypoxemia[32-34]. ERPs are partially generated in subcortical cerebral structures, providing a neurophysiological measure of brain dysfunction that is positively correlated with hypoxemia level. Therefore, we took a systematic approach, adopting a minimal SaO_2 level and persistent time as the index to assess obstructive sleep apnea hypopnea syndrome patients.

MoCA is a brief and sensitive tool for the assessment of cognitive impairment in obstructive sleep apnea hypopnea syndrome patients whose performance on the Mini-Mental State Examination is in the normal range. We found that MoCA scores decreased progressively as hypoxemia worsened. Evaluation of MoCA subdomains further revealed selective impairment of memory/delayed recall, visuospatial and executive function, and attention in the moderate-to-severe groups. These findings are in accordance with the majority complaints of obstructive sleep apnea hypopnea syndrome patients, and the abnormal characteristics reflected by mismatch negativity. Although the patients did not suffer from dementia, their symptoms affected their quality of life. In accordance with studies revealing a correlation between MoCA scores and minimum SaO_4 and number of years of education[35-37], hypoxemia is thought to be a leading factor[38-39]. In addition, we found a tendency for MoCA scores to decrease as mismatch negativity latency increased, with a Pearson correlation coefficient of $r = -0.791$ ($P < 0.05$). The prevalence rate tested by the two tests exhibited no significant difference, and the two tests showed better concordance.

The MoCA is typically considered the gold standard for examining mild cognitive impairment of obstructive sleep apnea hypopnea syndrome. However, mismatch negativity provides a way of detecting and diagnosing cognitive impairment in obstructive sleep apnea hypopnea syndrome patients that can differentiate mild cognitive impairment and normal subjects more effectively. In addition, mismatch negativity can sensitively identify patients with cognitive deficits, and can confirm and/or eliminate specific diseases. A previous study of cognitive impairment evaluation revealed that the sensitivity of ERP-P_3 was 84–96%, and specificity was 13–80%[40]. However, until now no standard diagnostic value of mismatch negativity has been reported. Because of its instability, ERPs are not commonly used as clinical diagnostic pathways. Our preliminary study was conducted primarily to examine the possibility of clinical use of mismatch negativity, and the current results revealed that mismatch negativity can detect brain dysfunction and can be used as an additional diagnostic tool in the examination of cerebral deficits in obstructive sleep apnea hypopnea syndrome patients.

Overall, we found that chronic intermittent nocturnal hypoxemia in obstructive sleep apnea hypopnea syndrome patients leads to cognitive deficits. The hypoxemia level and its persistent time appeared to function as appropriate indices of the severity of obstructive sleep apnea hypopnea syndrome effectively and objectively. The component of auditory event related potential mismatch negativity exhibits a strong correlations with the MoCA neurocognitive instrument, and represents an effective monitoring tool to detect brain dysfunction in patients with obstructive sleep apnea hypopnea syndrome.

SUBJECTS AND METHODS

Design

A case-controlled, neuro-electrophysiological study.

Time and setting

Experiments were performed from February 2009 to April 2011 in Beijing Chaoyang Hospital, China.

Subjects

Patients group

This study group consisted of 97 obstructive sleep apnea hypopnea syndrome patients who were diagnosed and treated in the Department of Otolaryngology Head and Neck Surgery, Beijing Chaoyang Hospital, Capital Medical University, China, the patients were diagnosed on the basis of their complaints, physical examination, and polysomnography monitoring according to the severity of hypoxemia[41]. Before testing, the patients were divided into three subgroups; a mild group ($n = 30$; 85% ≤ minimum SaO_2 ≤ 90%), moderate group ($n = 32$; 65% ≤ minimum SaO_2 < 85%), and severe group ($n = 35$; minimum SaO_2 < 65%).

Inclusion criteria: Patients were aged between 40 and 45 years; educational level was high school or higher;

had no treatment-experience; exhibited no visual disorders, and normal hearing. Patients were informed of the purpose of the experiment, and were cooperative.
Exclusion criteria: Patients with any neurological or psychiatric diseases (including depression); recent use of drugs known to affect sleep or daytime sleepiness such as antidepressants, hypnotics, history of brain traumatic injury. Since high blood pressure is a common feature in obstructive sleep apnea hypopnea syndrome patients, only patients with unstable high blood pressure were excluded.

Control group

Another 35 healthy controls (normal: Apnea Hypopnea Index < 5) were recruited from Beijing Chaoyang Hospital, Capital Medical University, China. They were matched to the patients in terms of age and gender. All controls exhibited good sleeping habits, normal hearing, no visual disorders, no psychiatric or nervous system diseases, and no recent use of drugs known to affect sleep or daytime sleepiness. All controls appeared to understand the purpose of the experiment, and were cooperative.
Each participant was informed of the research protocols. The protocol was approved by the *Declaration of Helsinki*.

Methods

Polysomnographic monitoring

All subjects underwent polysomnographic recording for at least 7 hours (from 10:00 p.m. to 7:00 a.m.) during nocturnal sleep in the sleep laboratory. Polysomnography (Embla N7000, Ft. Lauderdale, FL, USA) was performed, as well as electroencephalography, electrooculography, chin and leg electromyography and electrocardiography were synchronously and continuously recorded. As indices of hypoxemia, the mean SaO_2 and the minimal SaO_2 during sleep and the percentage of sleep time spent at SaO_2 below 90% (SaO_2 < 90%) were measured using a transcutaneous finger pulse oximeter. Thoracoabdominal plethysmograph and oronasal thermistors were used to monitor snoring position and respiration. After testing, all polysomnographic data were analyzed by trained technicians and/or physician specialists, including sleep architecture, apnea hypopnea index, average SaO_2, minimum SaO_2 duration time and level.

Mismatch negativity test

The test was conducted using a computer in an acoustic chamber room (in accordance with GB/T16403-199 requirements and electroencephalography was recorded using a bio-logic auditory evoked device (Bio-logic, Mundelein, IL, USA). According to the international brain electrical 10/20 system, electroencephalographic recordings were obtained from silver-plate electrodes at Fz midline scalp sites, reference electrodes attached to the right earlobe and ground electrodes attached to the left earlobe. The sound was presented through a headset, using a passive auditory model[42]. The subjects remained quiet and relaxed, and read self-selected favorite books, to help them ignore the sound stimulus. Subjects were given short pure tone stimulation, using an oddball stimulation sequence[1, 35], composed of high probability repeated standard stimuli (1 000 Hz) and low probability of deviant stimuli (2 000 Hz). In these categories, 80% of the stimuli were standard, and 20% of the stimuli were deviant, with the order of stimuli randomized. Stimulus intensity was 70 dB SPL, the schedule of stimuli was 50 ms and a total of 533 ms of stimuli was presented over 12 minutes. The rate of stimulus presentation was 1.10 per second, build up to 30 presentations. A band-pass filter of 0.1–30 Hz was applied, and impedance was kept below 5 kΩ. To avoid the effects of brain fatigue, all tests were conducted at 8:30–9:00 a.m. Subjects were allowed to relax for 10 minutes between the two tests.
The test was conducted by one trained technician. Each subject was tested twice, and mean values were calculated between each of two recording sites. Mismatch negativity waveform identification: the peak latency (ms) appeared during 100–250 ms from change onset to the largest mismatch negativity peak point of the horizontal axis. The amplitude (μV) ranged from a zero baseline to mismatch negativity peak potential.

MoCA scale

MoCA scale is typically used to screen mild cognitive impairment quickly and conveniently, for patients exhibiting normal Mini-Mental State Examination scores[43]. The MoCA scale is a 30-point test used to explore eight aspects of cognitive functions; these eight aspects were then subdivided into 12 topics and 30 single items, which comprehensively evaluated the function of visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall and orientation. Scores < 26 are considered to indicate mild neurocognitive impairment. Each correct answer is equal to one point, while an incorrect answer or no answer is equal to zero points. At the end of the test, we calculated scores for each subdomain, and for the total scale. To certify the reliability and accuracy of the MoCA, subjects underwent the test between 9:00–9:30 a.m., conducted by the same physician trained in psychology.

Statistical analysis

Data are presented as mean ± SD. Statistical analysis were performed using SPSS 13.0 software (SPSS, Chicago, IL, USA). One-way analysis of variance was used to compare mismatch negativity characteristics and

MoCA scores among the groups of subjects. With regard to the group comparison, one-sample *t* test was used to compare the influence of hypoxemia on mismatch negativity waveforms. Linear regression analysis with calculation of Pearson correlation coefficients (*r*) was used to evaluate the correlations between mismatch negativity and MoCA scores. The prevalence of cognitive impairment was detected by mismatch negativity and MoCA respectively. Comparisons were performed using chi-square tests, to analyze the diagnostic value of mismatch negativity. We then calculated the sensitivity, specificity, accuracy rate, positive/negative predictive value and positive/negative likelihood ratio. Statistical significance was defined as $P < 0.05$.

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Author contributions: Xiaohui Wen designed the experiment, screened the patients, explained the protocol and flow sheet to the patients, and conducted the auditory tests and mismatch negativity tests. All the other authors helped to adjust the test protocol. Ningyu Wang was responsible for revising the manuscript.

Conflicts of interest: None declared.

Ethical approval: This pilot was approved by the Ethics Committee of Beijing Chaoyang Hospital in China.

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