Measuring saccades can be a reliable, objective, sensitive and rapid way for cognitive impairment assessment

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Abstract

Background and Objectives

Among the elderly, dementia is a common and disabling disorder with primary manifestations of cognitive impairments. Diagnosis and intervention in its early stages is the key to effective treatment. Practically, the test of cognitive function relies mainly on neuropsychological tests, such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Although these tests are widely used at the present, there are noticeable shortcomings, e.g., the biases of subjective judgments from physicians and the cost of the labor of these well-trained physicians. Thus, advanced and objective methods are urgently needed to evaluate cognitive functions. Accumulative evidence indicates that the saccades in certain tasks are highly correlated with the performance in some cognitive functions. However, only a few studies directly compared saccades with the performance in neuropsychological tests depicted by their scores. Thus, the reliability of using saccades as a behavioral biomarker to evaluate cognitive functions has rarely been explored.

Methods

310 subjects performed three sequential designed oculomotor tasks, pro-saccade (PS), anti-saccade (AS) and memory-guided saccade (MGS) and the saccadic parameters including error rate, saccadic reaction time and spatial error are studied.

Results

In general, most saccadic parameters correlate well with the MMSE and MoCA scores. Moreover, some subjects with high MMSE and MoCA scores have very high error rates in performing these three tasks due to various errors in saccade control. The primary error types vary among tasks, indicating that different tasks assess certain specific brain functions preferentially. Thus, to improve the accuracy of evaluation through saccadic tasks, we built a weighted model to combine the saccadic parameters of the three saccadic tasks. The receiver operating characteristic (ROC) curve analysis shows that the discrimination between cognitive impairment patients and control subjects is better through the output of our model than the MMSE test.

Conclusion

Measuring saccades in multiple tasks could be a reliable, objective and sensitive method to evaluate cognitive function and thus to help diagnosing cognitive impairments.

Backgroud

Dementia is defined by a group of symptoms affecting memory, thinking and social abilities severely enough to interfere with one's daily life. It is one of the leading causes of disability in the elderly population worldwide, which places a huge burden on families and society, financially and

psychologically (1–3). Although some interventions for the treatment of dementia have already been developed, most of them aim to relieve symptoms and slow disease progression (4, 5). Unfortunately, no effective approach has been reported to cure this disease to date. An increasing number of studies have pointed out that the key to combating dementia is to diagnose and intervene at an early stage, such as at the stage of mild cognitive impairment (MCI) (6–8).

To date, the most frequently administered tests to evaluate cognitive functions for the diagnosis of MCI are neuropsychological scales, such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) (9, 10). Although these tests are widely accepted and used, they have noticeable deficiencies. First, they are not objective. The reported sensitivity and specificity of the MMSE and MoCA greatly vary among previous studies (11), which is mainly caused by the biases due to subjective judgments of physicians (12). Second, they are costly. Most neuropsychological tests need to be administered by well-trained physicians or general practitioners, which requires a considerable labor fee. Third, they are not timesaving. A simple test such as the MMSE usually takes 10–20 minutes to complete and tends to take even longer if subjects are old or have low education (13); this time spent is even worse for other complex tests such as the MoCA and ADAS-Cog (14). Thus, objective, economical, rapid and easily administered methods for evaluating cognitive function are urgently needed.

Saccades are rapid jerky movements of the eyes that congruently rotate the eyes to direct fovea of the retina to a position where the visual acuity is the highest for the objects of interest in the visual field (15). Saccades are not executed randomly but are goal driven (16). Indeed, the execution of each saccade might be affected by certain cognitive functions, such as attention, target selection, memory, decision and intention, which depend on the task context (17). It is well known that several brain areas are involved in the control of saccades, including cortical and subcortical areas (18–21). Damage to any of these areas lead to specific deficits in saccades during particular tasks that require the involvement of certain cognitive functions (22–25). Therefore, monitoring saccades under oculomotor tasks is a powerful way to assess the cognitive functions of the brain (17, 26). However, while most previous studies focused on understanding the deficits of saccades under cognitive impairments, very few studies directly compared the performance in saccadic tasks with the scores of neuropsychological tests (26–28). Thus, the clinical usability and reliability of evaluating cognitive functions via the analysis of saccadic eye movements have rarely been explored.

In the present study, we compared the saccadic parameters with MMSE and MoCA scores in three saccadic tasks. The correlation analysis shows that some saccadic parameters, e.g., the error rate, reaction time and spatial error (distance between the final saccadic endpoint and saccadic goal), correlate well with the MMSE and MoCA scores. In addition, some subjects with high MMSE and MoCA scores performed these three tasks poorly due to various errors in the control of saccades. Such results evidently demonstrate that, compared to the MMSE and MoCA tests, there is an advantage of the analysis of saccades, which additionally assesses motor-related cognitive functions. Finally, we built a model that comprehensively weighs the saccadic parameters of three saccadic tasks. The ROC curve analysis shows that both the area under the curve (AUC) and Youden index at the optimal cutoff point

with our model are larger than those of the MMSE score, which indicates that the diagnostic performance of our model is better than that of the MMSE test. Altogether, our results demonstrate that the analysis of saccades could be a reliable, objective and sensitive method to evaluate cognitive function and to help diagnose cognitive impairments.

Materials And Methods

Participants

We recruited five groups of subjects: 71 elderly healthy control subjects (EHC), 70 elderly subhealth control subjects (ESHC), 71 suspicious MCI subjects (SMCI), 71 MCI subjects and 27 dementia subjects. The sample size was ascertained by using GPower software, effect size = 0.4, $\alpha = 0.05$ and $\beta = 0.1$, and the power was $1-\beta = 0.9$(29). The EHC subjects did not have any symptoms of neurologic diseases, psychiatric diseases and cognitive deficits; their MMSE scores were ≥ 27. The ESHC subjects had complaints of mainly certain cognitive impairments, e.g., poor memory. and atypical neurological symptoms, such as continued dizziness, headache and insomnia, but no conspicuous cognitive deficits (MMSE score ≥ 27, MoCA score ≥ 24). SMCI subjects had abnormal scores on the MMSE or MoCA tests, but no remarkable symptoms of cognitive impairment (i.e., did not meet the diagnostic criteria of MCI according to the National Institute on Aging Alzheimer's Association workgroups in 2011 (30)). MCI subjects met the diagnosis criteria of MCI according to the previous criteria. Dementia subjects met the diagnosis criteria according to the National Institute on Aging-Alzheimer's Association workgroups (31). The demographic information of the subjects is provided in Table 1. All study protocols were approved by the Ethics Committee of The General Hospital of PLA. We performed all research according to the relevant guidelines and regulations, including the Declaration of Helsinki.

Table 1
Demographics

	EHC	ESHC	SMCI	MCI	Dementia	*P* value
Number of participates	71	70	71	71	27	
Age, years, mean (SD)	75.6 (4.4)	74.9 (8.6)	77.3 (8.9)	76.0 (9.1)	78.5 (8.5)	0.07
gender, male, n (%)	35 (49.3)	42 (49.3)	47 (66.2)	44 (62.0)	17 (63.0)	0.32
MMSE available	71	70	71	71	27	
MMSE, mean (SD)	28.8 (1.0)	28.5 (1.3)	27.0 (2.0)	24.7 (3.3)	17.2 (5.9)	< 0.001
MOCA available	5	60	69	67	26	
MOCA, mean (SD)	25.6 (2.6)	26.8 (1.5)	22.8 (2.2)	20.1 (3.4)	13.4 (4.5)	< 0.001
Model score available	71	70	71	71	27	
Model score, mean (SD)	65.2 (11.7)	56.2 (14.8)	43.9 (17.2)	29.3 (17.6)	5.9 (3.3)	< 0.001

We administered the MMSE and MoCA to evaluate the general cognition of all subjects, but most EHCs were only tested by the MMSE. The scores of both the MMSE and MoCA ranged from zero to 30, where a lower score indicated increased level of cognitive deficits.

Experimental setup

Subjects sat in a dark room with their heads restrained on a chin rest. Eye position was recorded by an infrared video-based eye tracker (EyeLink 1000 desktop mount, SR Research, Ltd., Ontario, Canada; EyeMind 2000, Jasmine Science and Technology Ltd., Chengdu, China). The sampling rate for both eye trackers were 1 KHz. All visual stimuli were displayed on a 27-inch LCD monitor (1920 × 1080 resolution, 100 Hz refresh rate) positioned 57 cm in front of the subjects. Visual stimuli presentation and behavioral data collection were controlled by MATLAB (R2009b; MathWorks, Natick, MA, USA) with Psychtoolbox (PTB-3) running on a Windows PC system (HP).

To avoid subjective biases on the evaluation of results, the neuropsychological tests (MMSE and MoCA) and saccadic eye movement experiments were performed by different individuals in a counterbalanced fashion. The experimenters were blinded to each other's results.

Behavioral tasks

Pro-saccade task (PS, Fig. 1A)

The trial begins with the appearance of a fixation point, FP (white cross, horizontal 1° × vertical 1° in size), at the center of the screen. Subjects need to look at it as soon as it appears. If the subjects' eyes enter a

check window (4° in radius) and stay within the window for 800 ms, the FP disappears and a visual cue (white dot, diameter 1° in size) simultaneously appears at one of four peripheral locations randomly (left, right, up and down; at eccentricity of 10°). Subjects are instructed to make a saccade toward the visual cue as accurately and rapidly as possible. The visual cue disappears after the eyes enter and stay within a check window (4° in radius) for 800 ms. If the subjects' eyes do not enter the fixation window 1000 ms after FP onset or if the subjects do not make a saccadic eye movement 2000 ms after the visual cue onset, the trial is aborted. At the end of each trial, there is an 800 ms inter trial interval (ITI), in which a blank screen appears.

Anti-saccade task (AS, Fig. 1B)

The event sequence in AS is the same as that of PS, except that the subjects are instructed to make a saccade in the opposite direction of the visual cue (mirror location).

Memory-guided saccade task (MGS, Fig. 1C)

The trial begins with the appearance of a FP at the center of the screen. Subjects need to look at it as soon as it appears. If the subjects' eyes entera check window (4° in radius) and stay within the window for 800 ms, a cue appears at one of four peripheral locations randomly (same as in PS) for 500 ms. The subjects are instructed to keep their fixation at the FP and remember the cued location. The disappearance of the cue is followed by a delay period (1000 ms or 600 ms), during which, the subjects need to keep their fixation at the FP. The disappearance of FP serves as a "go signal", which indicates that the subjects need to make a saccade toward the remembered cue location as accurately and as rapidly as possible. The trial finishes after the eyes enter and stay within the cue check window (4° in radius) for 800 ms. Otherwise, if subjects' eyes do not enter the fixation window 1000 ms after FP onset, the trial is aborted. Similarly, if subjects do not make a saccadic eye movement 2000 ms after the "go signal", the trial is again aborted. If the subjects moved their eyes out of the check window of FP while FP is on, the trial ends as a "fixation break". At the end of each trial, there is an ITI of 800 ms, in which the blank screen appears.

Data analysis

Analysis of reaction time, spatial error and trial types

The reaction time was calculated as the time interval between the go signal (the disappearance of FP) and the start of the first responsive saccade (amplitude is greater than 2° and direction is within ± 45° of saccadic goal). The spatial error was calculated as the distance between the endpoint of the last responsive saccade and the goal location.

Trials are classified into six types, including correct trial, aborted trial, missing trial, fixation break trial, spatial error trial and uninhibited reflexive saccade trial (only in AS and MGS). The correct trial refers to the trials in which subjects perform the task by perfectly following the requirement. The aborted trial refers to trials in which subjects do not move their eyes into the fixation window within 1000 ms after FP

onset. The missing trial refers to the trials in which subjects do not make saccades within 2000 ms after FP offset. The spatial error trial refers to the trial in which the distance between the final saccadic endpoint and goal location is larger than the mean spatial error plus 1.96 times the standard deviation of EHC subjects, and each task has its own spatial error threshold. The unsuppressed reflexive saccade trial refers to the trials in which subjects make saccades to the location of visual cues either in the wrong direction (in AS) or at the wrong time (in MGS), according to the task requirement.

The mean reaction time and spatial error are calculated for a subject only if the number of trials with responsive saccades are ≥ 10% of all trials. We raise this criterion to 20% and 25%, and the results of the correlation analysis between these two parameters and MMSE or MoCA scores are similar to the criterion of 10%.

The principle to build the weighted multiple saccadic parameters model

To improve the accuracy of cognitive function assessment by measuring saccades, we build a multiplicative model in which the saccadic parameters and the three tasks are weighted based on their contributions in discriminating patients from control subjects. To prevent “overfitting” that might be caused during training, we randomly divide our data into two equal parts for training and testing. The training process repeats five times, as follows:

For each task, we first determine the saccadic parameters that correlate with MMSE and MoCA scores. Then, we normalize each of these parameters (K_i) to standardize it in the range from zero to one, based on the range of its distribution among the subject population. After that, if it is the first time for model training, we assign each K_i a coefficient (W_i) and set W_i as one for initialization. Otherwise, W_i was set as the value in the last model. If there are n parameters in a task, according to the principle of the multiplicative model, the score for this task (S) is calculated as follows:

$$S = \prod_{i=1}^{n} W_i K_i$$

1

We systematically adjust the coefficient W_i for each K_i to make S reach the largest area under the curve (AUC in the ROC curve analysis that examine the likelihood of S in discriminating patients from control subjects (see statistical analysis for details).

After determining the W_i for each K_i in each task, we weight the contribution of each task (S_i) by multiplying a coefficient P_i. If it is the first time of model training, P_i is set as one for initialization. Otherwise, P_i is set as the value in the last model. According to the principle of the multiplicative model, the score (M) of multiple tasks (n) is calculated as follows:

$$M = \prod_{i=1}^{n} S_i P_i$$

2

We systematically adjust the coefficient P_i for each S_i to make the M reach its largest AUC in the ROC curve analysis.

Statistical analysis

Spearman's rank correlation is applied to determine the correlation between saccadic parameters in the three saccadic tasks and the MMSE and MoCA scores. The values of *p* and *r* in the correlation analysis indicate the significance and correlation coefficient of the regression fitting.

We use ROC curve analysis to test the likelihood of discriminating patients with cognitive impairment from control subjects either by analysis of saccades or by MMSE scores. The AUC and Youden index at the optimal cut-off point are used as indices to indicate the degree of discrimination.

All statistical analyses in the present study are performed by MATLAB (R2017a; MathWorks, Natick, MA, USA), except for the ROC curve analysis, which is performed by MedCalc statistical software v20 (MedCalc Software Ltd, Acacialaan 22, B-8400 Ostend, Belgium).

Data availability

Available when required

Results

The error rate, reaction time and spatial error in the three tasks correlate with MMSE and MoCA scores, respectively:

An intuitive way to examine the reliability of a novel technique is to make comparisons with well-established systems. Thus, we first seek to determine whether there is a correlation between the performance of saccades in the three tasks and MMSE and MoCA scores. Here, we focus our analysis on three saccadic parameters, i.e., the error rate, reaction time and spatial error, because they reflect the capability, efficiency and accuracy of a subject to perform the tasks. In MGS, there are two different delay intervals (1000 and 600 ms). The 600 ms delay is only used in 41 patients at the beginning of this experiment. Since there was no significant difference in error rate, reaction time or spatial error between the two groups of subjects who performed MGS with 1000 ms or 600 ms delays, their data are combined for further analysis.

The results of the correlation analysis between error rates and MMSE and MoCA scores in the three tasks are shown in Fig. 2. Notably, the error rates in all three tasks are negatively correlated with MMSE and MoCA scores, which indicates that the majority of subjects with higher MMSE and MoCA scores have a

higher capability to perform the saccadic tasks, and vice versa. However, the correlation is much weaker in PS (MMSE: $p < 0.01$, $r = -0.15$, Fig. 2A; MoCA: $p < 0.01$, $r = -0.11$, Fig. 2B) than in AS (MMSE: $p < 0.01$, $r = -0.44$, Fig. 2C; MoCA, $p < 0.01$, $r = -0.50$, Fig. 2D) and MGS (MMSE, $p < 0.01$, $r = -0.44$, Fig. 2E; MoCA, $p < 0.01$, $r = -0.49$, Fig. 2F). Moreover, there are subjects with low MMSE and MoCA scores who have a low error rate in PS but not in AS or MGS. Such results are understandable because correctly performing PS requires the involvement of a very limited cognitive function, if at all. In contrast, correctly performing AS and MGS requires the involvement of more cognitive functions, e.g., inhibition, spatial calculation and working memory. Thus, the error rates in AS and MGS reflect the state of cognitive functions more veritably than in PS.

Moreover, the reaction times and spatial errors are also negatively correlated with both MMSE and MoCA scores. The results of the correlation analysis are presented in Figs. 3 and 4, respectively. The figure formats are the same as in Fig. 2. While reaction times weakly but significantly correlated with MMSE and MoCA scores in PS (MMSE: $p < 0.01$, $r = -0.18$, Fig. 3A; MoCA: $p < 0.01$, $r = -0.26$, Fig. 3B) and AS (MMSE: $p < 0.01$, $r = -0.21$, Fig. 3C; MoCA, $p < 0.01$, $r = -0.24$, Fig. 3D), the correlation did not reach a significant level in MGS (MMSE, $p = 0.06$, $r = -0.01$, Fig. 3E; MoCA, $p = 0.15$, $r = 0.06$, Fig. 3F). Considering the fact that the process of visuomotor transformation may have been completed during the delay interval in MGS, the reaction time in MGS is not proper to examine the efficiency of signal transformation. In addition, the standard deviation of reaction times in the three tasks are all negatively correlated with the MMSE and MoCA scores (Fig. 3G-L). Such results indicate that subjects with higher MMSE and MoCA scores generally have higher efficiency and less variation to transform the signal from sensory input to motor output.

The spatial errors in the three tasks show a weak but significant correlation with both the MMSE and MoCA scores. The results of the correlation analysis are shown in Fig. 4A (MMSE: $p < 0.01$, $r = -0.10$) and 4B (MoCA: $p < 0.01$, $r = -0.09$) for PS; in Fig. 4C (MMSE: $p < 0.01$, $r = -0.14$) and 4D (MoCA: $p < 0.01$, $r = -0.16$) for AS; and in Fig. 4E (MMSE: $p < 0.01$, $r = -0.22$) and 4F (MoCA: $p < 0.01$, $r = -0.26$) for MGS. In addition, the standard deviation of spatial errors in the three tasks all negatively correlated with the MMSE and MoCA scores (Fig. 4G-L). Such results indicate that subjects with higher MMSE and MoCA scores generally have higher spatial accuracy (i.e., lower spatial error) and less variation to perform saccadic tasks.

A group of subjects have high MMSE and MoCA scores but also a high error rate in three saccadic tasks:

Interestingly, the results of correlation analysis show that a group of subjects with high MMSE and MoCA scores (MMSE score ≥ 27, MoCA score ≥ 24) have very high error rates in the three saccadic tasks. To understand the reasons behind what may have caused such inconsistency, we separated the subjects with high MMSE and MoCA scores into two groups based on their error rates in each saccadic task. The classifying criterion is set as the mean error rate of these subjects minus one standard deviation. The red and blue rectangles in Fig. 5A, 5F and 5J show the separated two groups of subjects, respectively, i.e., group one with an error rate lower than the criterion and group two with an error rate higher than the

criterion. Next, we investigate the reasons for the high error rate in subjects of group two by analyzing the error types of saccades in the three tasks. We found that the primary error in PS was the inaccurate saccadic endpoint related to the saccadic goal location, i.e., the spatial error (Fig. 5B). Two exemplified sessions of eye traces from a normal subject (upper panel in Fig. 5C) and a subject with a high error rate show that the spatial error in the later subject (lower panel in Fig. 5C, magenta traces) is larger than that of the former subject. This phenomenon is also true for the averaged spatial error analysis between the two groups of subjects ($p < 0.01$, rank sum test, Fig. 5D).

The primary error type of group two subjects in AS is the unsuppressed reflexive saccade toward the location of the visual cue (Fig. 5F). Two exemplified sessions of eye traces from a normal subject (upper panel in Fig. 5G) and a subject with a high error rate show that the unsuppressed reflexive saccade occurs more frequently in the later subject (lower panel in Fig. 5G, brown traces) than in the former subject. This phenomenon is also true for the averaged rate analysis of unsuppressed reflexive saccades between the two groups of subjects ($p < 0.01$, rank sum test, Fig. 5H).

Unlike PS and AS having a single primary error type, there are three major error types for group two subjects in MGS, including spatial error, missing error and error of unsuppressed reflexive saccade (Fig. 5J). Four examples of eye traces are shown in Fig. 5K. From top to bottom, each panel represents eye traces from a normal subject, a subject making a large proportion of spatial errors (magenta traces), a subject making the greatest number of missing errors (green traces) and a subject making a large proportion of unsuppressed reflexive saccades (brown traces). The average rates of the three error types are significantly higher in group two subjects than in group one subjects ($p < 0.01$, rank sum test, Fig. 5L).

The results of saccadic error type analysis from the data of three tasks indicate that (1) compared with MMSE and MoCA tests, the remarkable advantage of measuring saccades is the ability to test movement-related functions; (2) each of these three tasks preferentially tests different cognitive and saccade related functions. Thus, we assume that the accuracy of evaluating brain function by analyzing combined saccadic parameters in multiple saccadic tasks is higher than that of a single saccadic parameter in a single task.

The discrimination of different groups of subjects is better using the combination of saccadic parameters from multiple tasks than a single saccadic parameter in a single task:

To examine the assumption that the evaluation of brain function with the combination of saccadic parameters from multiple tasks is more accurate than a single saccadic parameter in a single task, we build a weighted multiple saccadic parameter model (see methods for details). Then, we compare the efficiency of the model with the two most sensitive parameters (error rates in AS and MGS) in discriminating different groups of subjects. While both error rates in AS and MGS can discriminate different groups of subjects other than ESHC and SMCI (Fig. 6A-B), the output of the model can discriminate all five groups of subjects (Fig. 6C). Moreover, an ROC curve analysis shows that the discrimination of patients with cognitive impairment (MCI and dementia) from EHC is better by using the output of the model (AUC = 0.961, 95% CI 0.920–0.985) than the error rate in AS (AUC = 0.918 95% CI

0.865–0.954) and MGS (AUC = 0.909 95% CI 0.855–0.948; pairwise comparison of ROC curves by z test: AS error rate vs. model score, $p = 0.0061$, MGS error rate vs. model score, $p = 0.0058$) (Fig. 6D). In addition, the discrimination of patients with cognitive impairment (MCI and dementia) from the remaining three groups of subjects (EHC, ESHC and SMCI) is better using the output of the model (AUC = 0.892, 95% CI 0.853–0.925) than the error rate in AS (AUC = 0.836 95% CI 0.790–0.875) and MGS (AUC = 0.839 95% CI 0.793–0.878; pairwise comparison of ROC curves by z test: AS error rate vs. model score, $p = 0.0003$, MGS error rate vs. model score, $p = 0.0077$) (Fig. 6E). These results support our previous assumption.

The diagnostic performance of saccade measurements is more accurate than the MMSE test:

We directly compared the diagnostic performance between the output of our model and the MMSE test by employing ROC curve analysis, to assess the likelihood of discriminating patients with cognitive impairment from control subjects. When discriminating patients with cognitive impairment (MCI and dementia) from EHC, our model showed better accuracy (model: AUC = 0.961, 95% CI 0.920–0.985, Youden index at the optimal cutoff point = 0.802, sensitivity = 81.63%, specificity = 98.59%; MMSE: AUC = 0.919, 95% CI 0.867–0.956, Youden index at the optimal cutoff point = 0.745, sensitivity = 74.49%, specificity = 100%). Pairwise comparison of ROC curves by z test between the model and MMSE resulted with $p = 0.0680$. (Fig. 7A). When discriminating patients with cognitive impairment (MCI and dementia group) with the remaining three groups (EHC, ESHC and SMCI), our model showed better accuracy (model: AUC = 0.892, 95% CI 0.853–0.925, Youden index at the optimal cutoff point = 0.664, sensitivity = 86.79%, specificity = 79.59%; MMSE: AUC = 0.865, 95% CI 0.853–0.925, Youden index at the optimal cutoff point = 0.603, sensitivity = 85.85%, specificity = 74.49%). However, pairwise comparison of ROC curves by z test between the model and MMSE resulted with $p = 0.3017$. (Fig. 7B).

Finally, there were 27 cognitive impairment patients with positive positron emission tomography (PET) beta-amyloid accumulation imaging test results. These 27 patients met the research diagnosis criteria of MCI due to AD according to the National Institute on Aging Alzheimer's Association workgroups in 2011 (30). Among these 27 patients, our model resulted in a true positive rate of 92.6% (25 out of 27), while the MMSE resulted in a true positive rate of 85.2% (23 out of 27).

Taken together, the results mentioned above, to some extent, indicate that the diagnostic performance of measuring saccades is better than that of the MMSE test, although some of results do not reach statistical significance.

Discussion

In the present study, we directly compare the performance of saccades in three saccadic tasks with the scores of MMSE and MoCA tests. The correlation analysis shows that the error rate, reaction time, spatial error, standard deviation of reaction time and spatial error are all negatively correlated with the scores of the MMSE and MoCA tests (Fig. 2–4). Such results support the previous findings that the performance of

saccades is affected by cognitive functions (17), and the measurement of saccades can be a useful tool to evaluate the state of cognitive functionality (17, 26). Moreover, the correlation analysis shows that some subjects with high scores on the MMSE and MoCA tests performed saccadic tasks poorly due to various saccadic errors, including spatial error in PS, unsuppressed reflexive saccades in AS, spatial error, missing error and unsuppressed reflexive saccades in MGS (Fig. 5). It is well known that brain function can be generally classified into two categories, i.e., functions that are sensory-related or movement-related (32). Since MMSE and MoCA tests do not carefully examine the movement -related functions, such as motor suppression, motor preparation and motor execution, evaluating brain function by measuring saccades compensates for this shortcoming.

Another finding of the present study is that the accuracy of discriminating different groups of subjects is higher when combining the saccadic parameters of three saccadic tasks instead of using single saccadic parameters in a single task (Fig. 6). Moreover, both the ROC curve analysis and the comparison with the result of PET show that the discrimination between cognitive impairment patients and control subjects is better by using the output of our model than MMSE scores (Fig. 7).

Altogether, our results suggest that comprehensive analysis of saccadic parameters in multiple tasks could be a reliable, objective and sensitive method to evaluate cognitive function and thus help in diagnosing cognitive impairments. Since the measurement and analysis of saccades are performed by the eye tracking device and data analysis software, evaluating cognitive functions through the analysis of saccades is more objective, economic and effective than neuropsychological scales.

The rationale for evaluating cognitive functions by measuring saccades:

Accumulative evidence indicates that a wide-range of brain structures, including cortical and subcortical regions, are involved in various cognitive functions (33). Damage to any part of these structures will cause specific impairment of cognition (22–25). Thus, an ideal system to evaluate cognitive function should be able to measure the function of broad brain regions synthetically. Consistently, a large number of brain regions, including the frontal eye field (FEF), supplementary eye field (SEF), lateral intraparietal area (LIP), basal ganglia (BG), cerebellum, superior colliculus (SC) and brainstem, are involved in the control of saccades (15, 20, 21, 34–39). More importantly, many of these regions are also critically involved in various cognitive functions. For instance, the fronto-parietal loop, cortico-basal ganglia-thalamo-cortical loop (CBGTC loop), cerebellum and SC are important structures that are involved in many cognitive functions ranging from basic to sophisticated, e.g., attention, memory, intention, categorization and decision making(40–45). Thus, evaluating cognitive function by measuring saccades might be an ideal system.

The advantage of employing multiple saccadic tasks, such as PS, AS and MGS, in evaluating cognitive function:

Since performing different saccadic tasks requires the involvement of different brain regions and neural circuits, a combination of complementary tasks will extend the range of brain structures to be tested, therefore increasing the accuracy of evaluation.

Among the three tasks in the present study, the PS is the simplest. At the very least, the brain regions that are involved in the performance of PS, include the visual pathway from the retina to the primary visual cortex, the LIP (38, 39, 46), the SC (47) and oculomotor structures in the brainstem (48). Although performing PS requires the involvement of minimal cognitive function, as a “reflexive movement” task, the analysis of its saccadic parameters can help us to evaluate the function (e.g., efficiency and stability) of fundamental visual and saccadic pathways.

In contrast to PS, performing AS and MGS requires the involvement of broad oculomotor structures in higher cortical and subcortical regions, such as the prefrontal cortex (PFC), posterior parietal cortex (PPC), BG and cerebellum. (49, 50) While multiple cognitive functions are involved in performing both AS and MGS (51, 52), AS particularly tests the inhibition function (26, 53, 54), whereas MGS tests the function of working memory (55, 56). Thus, we believe that the combination of these three complementary tasks extends the range of brain structures to be tested, and therefore raises the accuracy of evaluation. Indeed, our results show that the discrimination of different groups of subjects is better by using the combination of saccadic parameters from multiple tasks than a single saccadic parameter in a single task (Fig. 6A-C), which supports our assumption.

The advantage of evaluating cognitive functions by measuring saccades instead of MMSE and MoCA test:

Compared to MMSE and MoCA tests, the most remarkable advantage of measuring saccades is to test the motor-related cognitive functions, e.g., inhibition, spatial working memory, spatial calculation and movement execution. The traditional neuropsychological scales mostly act in the form of “ask and answer”, thus scarcely evaluating motor-related cognitive functions. This advantage is evidently supported by the results of our correlation analyses between the error rates in saccadic tasks and MMSE and MoCA scores (Fig. 2), in which there are a group of subjects with high MMSE and MoCA scores but with also very high error rates. Further analyses show that the high error rates are caused by saccade-related errors, including spatial, inhibition, and missing errors (Fig. 5). As motor-related cognitive functions are one of the most important functions of the brain and they may be impaired in the early stage of brain diseases, measuring saccades extends the range of brain regions to be tested compared to those in MMSE and MoCA tests.

Another remarkable advantage of measuring saccades is its objectivity in evaluating cognitive functions. In contrast to MMSE and MoCA tests that are largely dependent on the subjectivity of the physicians (12), measuring saccades is dependent on the equipment of the eye tracker to monitor and collect eye position signals, and the data are analyzed by programed software.

Finally, evaluating brain function by measuring saccades saves time and money. Most neuropsychological tests need to be administered by well-trained physicians or general practitioners, which requires a considerable labor fee. Moreover, even a simple test such as the MMSE usually takes 10–20 minutes to complete and tends to take an even longer time if subjects are old or have low education (13). In contrast, measuring saccades only requires the subjects to sit in front of the screen and spend less than 10 minutes finishing each task according to the instructions. There is no need for well-trained physicians to carry out the tests.

Comparison between the present study and previous ones

Early in 1992, the eye movement task, especially the saccade task, was proposed as a noninvasive paradigm for cognitive assessment (54, 57–60). Most studies showed that MCI patients suffered from shorter fixation periods (61), less accuracy, longer reaction time, increased number of multiple step saccades (61–63) and higher AS error rates (53, 64). There were also a few studies directly comparing the error rates in AS with the MMSE scores, which reported that they were negatively correlated (26, 28, 53, 65). First of all, our results support the findings of these previous studies. On the other hand, there are several remarkable advantages in our present study compared to the previous ones. First, while previous studies usually focused on making comparisons between a specific saccadic parameter in a single task and the MMSE score, we systematically compare the multiple saccadic parameters in three saccadic tasks with MMSE and MoCA scores. Moreover, we build a comprehensively weighted model to combine multiple saccadic parameters in three saccadic tasks to raise the accuracy of the evaluation of cognitive function by measuring saccades. Our results show that the diagnostic performance of our model is more accurate than the single parameter of saccade (Fig. 6). Second, we observe that some subjects with high MMSE and MoCA scores showed a very high error rate in performing these three tasks due to various errors in saccade control. To the best of our knowledge, such a phenomenon has not been reported previously. A possible reason may be the relatively small number of subjects in previous studies; thus, the outliers were ignored. Third, considering the fact that the most remarkable feature of neurodegenerative diseases is gradual progression, in the real world, there is no clean-cut way to simply separate the elderly into healthy and diseased groups based on the status of cognitive function. This stratification of subjects is especially difficult when it is considered that there is a reasonably large variation in cognitive function within these two groups. However, most of the previous studies only include healthy and diseased subjects but ignore the subhealth population. In contrast, our study includes subhealth subjects (ESHC and SMCI groups), making our findings more reliable and more suitable to apply to real clinical practice than others.

Limitations and future plans

As a cognitive function evaluation system, the saccadic tasks included in the present study are relatively few. We are trying to add more tasks that are designed for the assessment of specific cognitive functions such as memory capacity and attention, etc. With the help of these tasks, we believe that the sensitivity and specificity will be improved in dissociating patients with cognitive impairment and healthy subjects. .

Another limitation of the present study is that the most of the EHC subjects do not complete MoCA test. This makes the comparison between measuring saccades and MoCA tests incomplete. We will improve this deficiency in the future studies.

Conclusion

Measuring saccades in multiple tasks could be a reliable, objective and sensitive method to evaluate cognitive function and thus to help diagnosing cognitive impairments.

Abbreviations

MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; PS = pro-saccade task; AS = anti-saccade task; MGS = memory-guided saccade task; ROC = the receiver operating characteristic; AUC = the area under the curve; MCI = mild cognitive impairment; EHC = elderly healthy control; ESHC = elderly sub-health control; SMCI = suspicious MCI; FP = fixation point; ITI = inter trial interval; MCI = mild cognitive impairment; PET = positive positron emission tomography; SEF = supplementary eye field; LIP = lateral intraparietal area; BG = basal ganglia; SC = superior colliculus ; CBGTC loop = cortico-basal ganglia-thalamo-cortical loop; PFC = prefrontal cortex; PPC = posterior parietal cortex

Declarations

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Author contributions

Mingsha Zhang, and Xuemei Li designed the experimental paradigms; Min Li, Junru Wu, Wenbo Ma, and Zhihao Zhang performed the experiments and analyzed the data; Mingsha Zhang and Xuemei Li supervised the experiments; Junru Wu and Mingsha Zhang wrote the manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical Approval and Consent to participate

All participants provided signed informed consent approved by the General Hospital of PLA.

Consent for publication

Not applicable

Competing interests

The authors report no competing interests.

Author information

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Figures

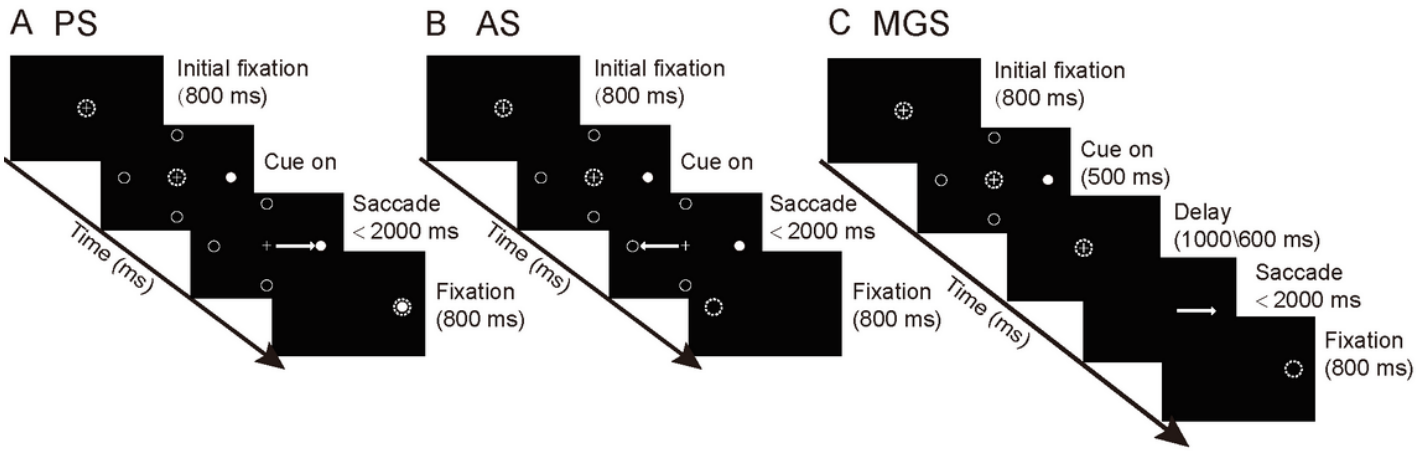

Figure 1

Schematic illustration of saccadic tasks. The cross represents the fixation point (FP). The dashed circle represents the required fixation location. The filled circle represents the cue. The open circles represent the potential cue locations. The arrow represents the required saccade trajectory. (**A**) Pro-saccade task (PS); (**B**) Anti-saccade task (AS); (**C**) Memory-guided saccade task (MGS).

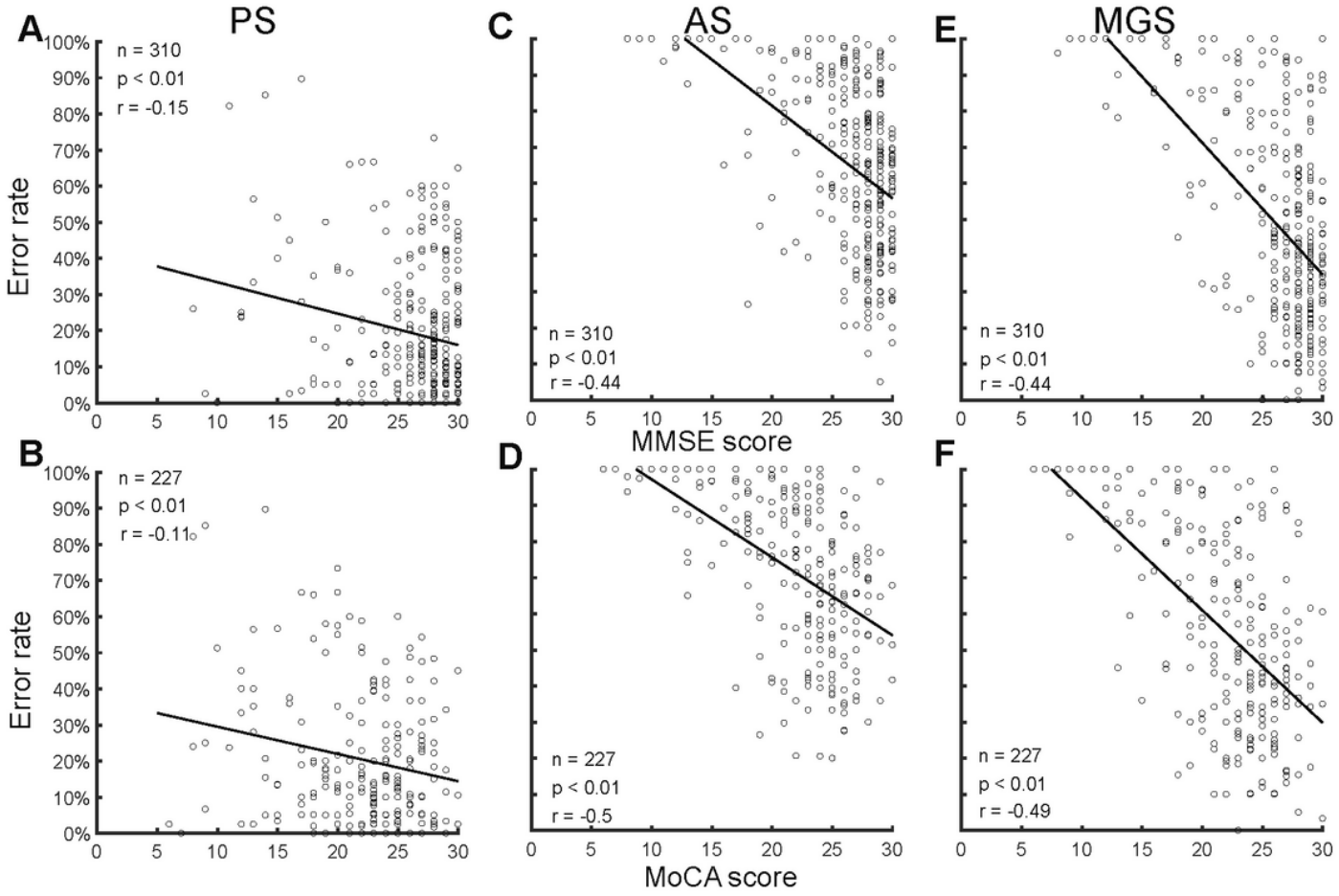

Figure 2

Correlation analysis between error rates and scores of MMSE and MoCA tests in three saccadic tasks. In each panel, an open circle represents the correlation result of an individual subject. Each black line represents the result of linear regression for the correlated data. The values of p and r in the correlation analysis indicate the significance and correlation coefficient of the regression fitting. (**A, B**) The correlation between the error rate in PS and scores of MMSE and MoCA tests. (**C, D**) The correlation between the error rate in AS and scores of MMSE and MoCA tests. (**E, F**) The correlation between the error rate in the MGS and scores of MMSE and MoCA tests.

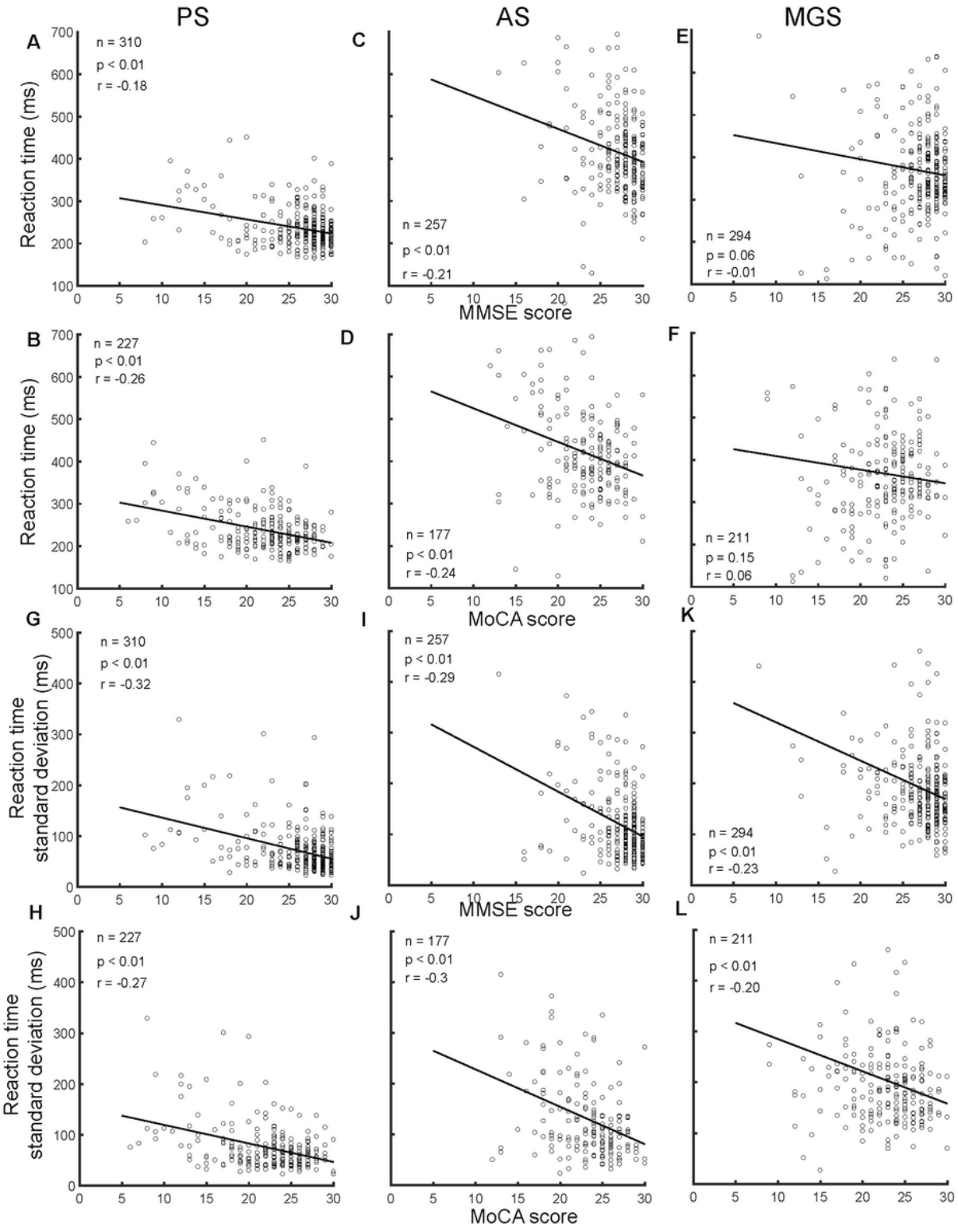

Figure 3

The correlation analysis between reaction time, its standard deviation and scores of MMSE and MoCA tests in three saccadic tasks. The figure format is the same as in Figure 2. (**A, B**) The correlation between reaction time in PS and scores of MMSE and MoCA tests. (**C, D**) The correlation between reaction time in AS and scores of MMSE and MoCA tests. (**E, F**) The correlation between reaction time in MGS and scores of the MMSE and MoCA tests. (**G, H**) The correlation between the standard deviation of reaction time in

PS and scores of MMSE and MoCA tests. (**I, J**) The correlation between the standard deviation of reaction time in AS and scores of MMSE and MoCA tests. (**K, L**) The correlation between the standard deviation of reaction time in the MGS and scores of the MMSE and MoCA tests.

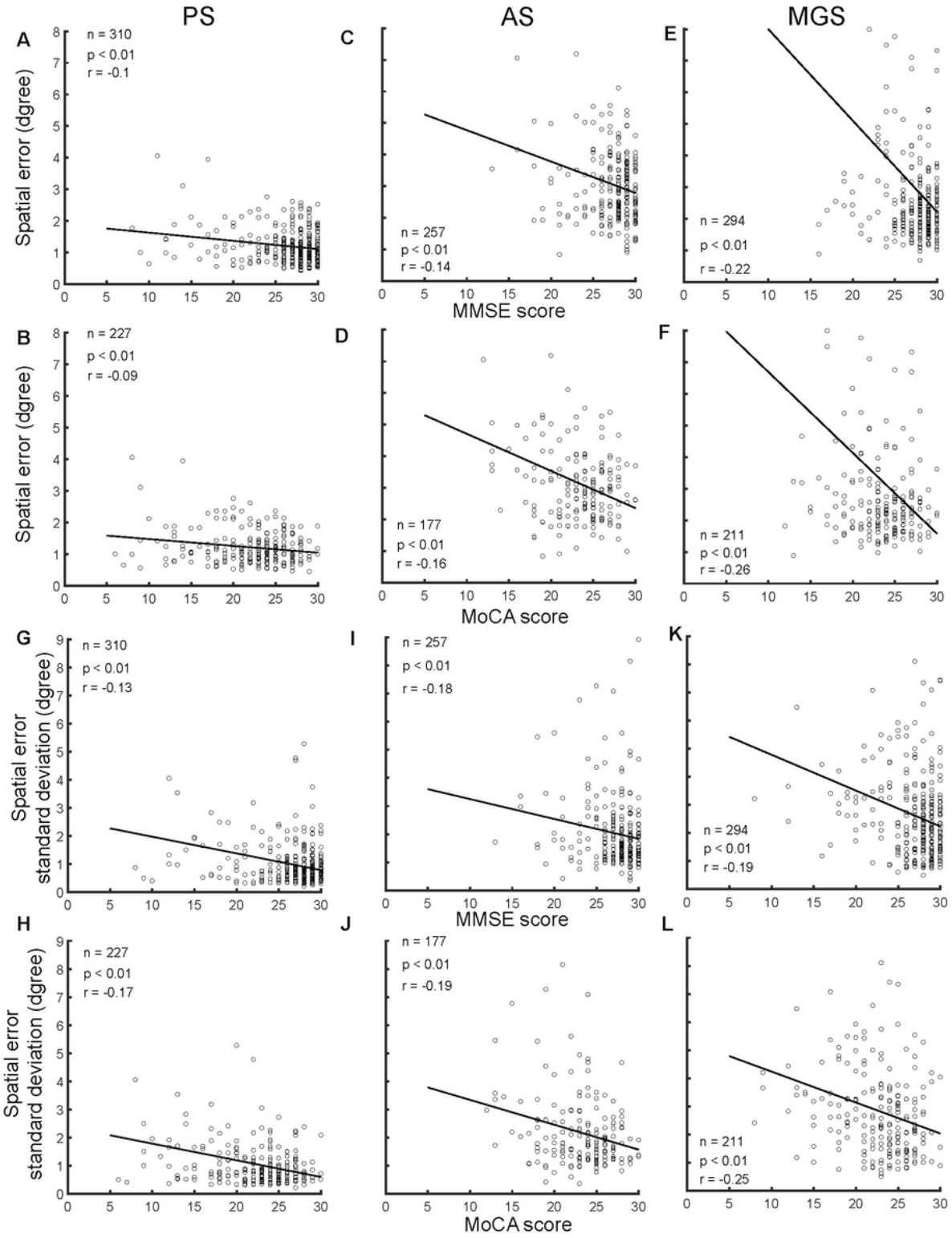

Figure 4

The correlation analysis between spatial error, its standard deviation and scores of MMSE and MoCA tests in three saccadic tasks. The figure format is the same as in Figure 2. (**A, B**) The correlation between spatial error in PS and scores of MMSE and MoCA tests. (**C, D**) The correlation between spatial error in AS and scores of MMSE and MoCA tests. (**E, F**) The correlation between spatial error in MGS and scores of MMSE and MoCA tests. (**G, H**) The correlation between the standard deviation of spatial error in PS and scores of MMSE and MoCA tests. (**I, J**) The correlation between the standard deviation of spatial error in AS and scores of MMSE and MoCA tests. (**K, L**) The correlation between the standard deviation of spatial error in MGS and scores of MMSE and MoCA tests.

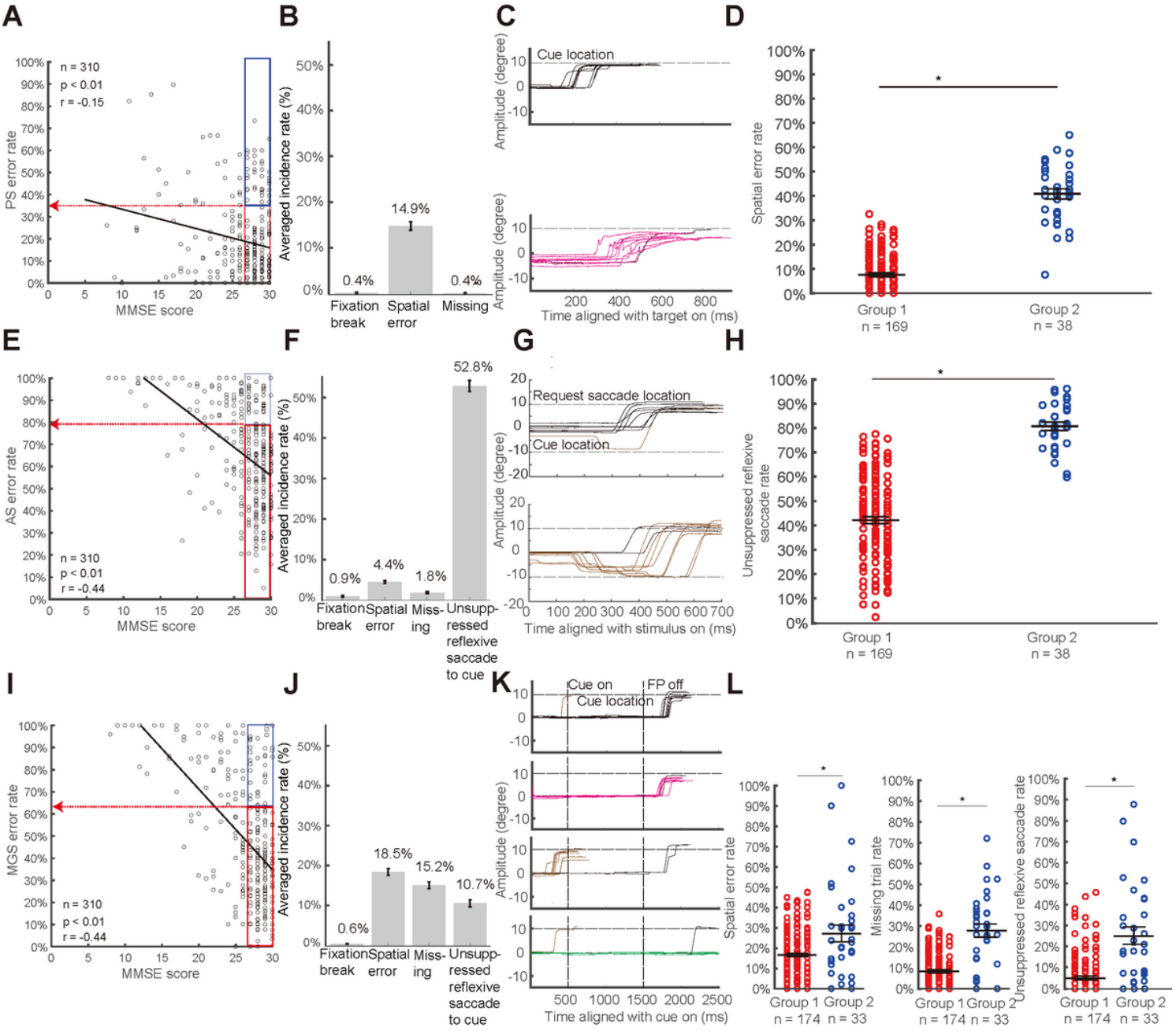

Figure 5

The error types in subjects with high MMSE and MoCA scores but low error rate in three saccadic tasks. (**A, E, I**). Subjects with MMSE scores ≥ 27 were classified into two groups. The classification criteria were set as the mean error rate of these subjects minus one standard deviation. The red and blue rectangles cover the two separate groups of subjects in the three tasks. (**B, F, J**) Analyzing the saccadic error types in three tasks. (**C, G, K**) Exemplified eye traces in three tasks. (**D, H, L**) Comparison of the error rates between the two groups of subjects in three tasks. Rank sum test, $p < 0.01$.

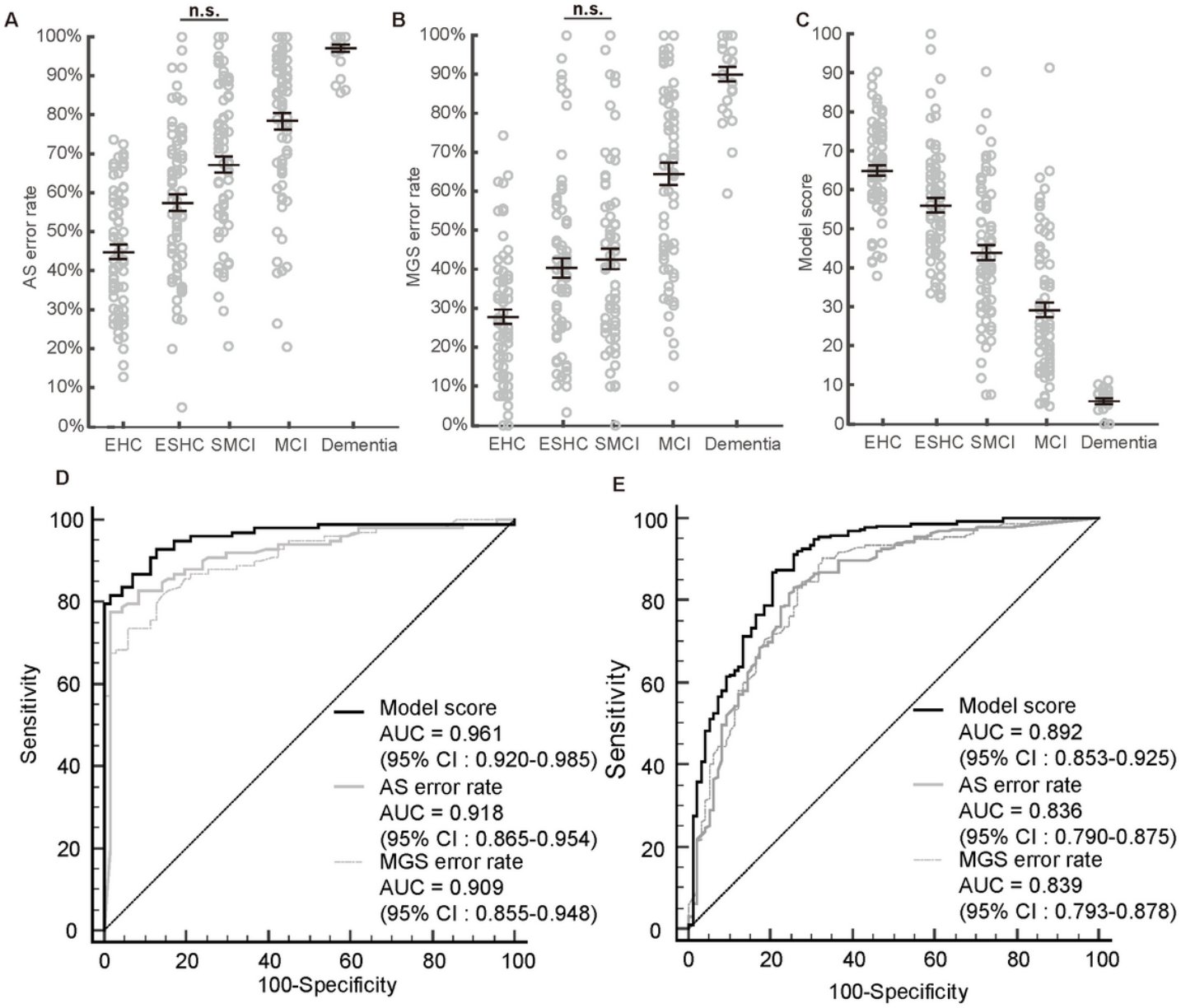

Figure 6

Comparison of discriminating accuracy between a combination of saccadic parameters from multiple tasks and a single saccadic parameter in a single task for five groups of subjects. (**A**) Discriminating by the error rate in AS. (**B**) Discriminating by the error rate in MGS. (**C**) Discriminating by the combination of saccadic parameters from multiple tasks (model score). In panels A-C, error bars represent SEM. Kruskal–

Wallis analysis was followed by the Tukey–Kramer multiple comparisons test. The difference between the two datasets was considered significant at $p < 0.05$, n.s. denotes no significant difference. (**D**) ROC curve analysis of the discrimination between subjects with cognitive impairment (MCI + dementia) and EHC by the output of the model and error rate in AS and MGS, respectively. (**E**) ROC curve analysis of the discrimination between subjects with cognitive impairment (MCI + dementia) and the remaining three groups (EHC + ESHC + SMCI) by the output of the model and error rate in AS and MGS, respectively.

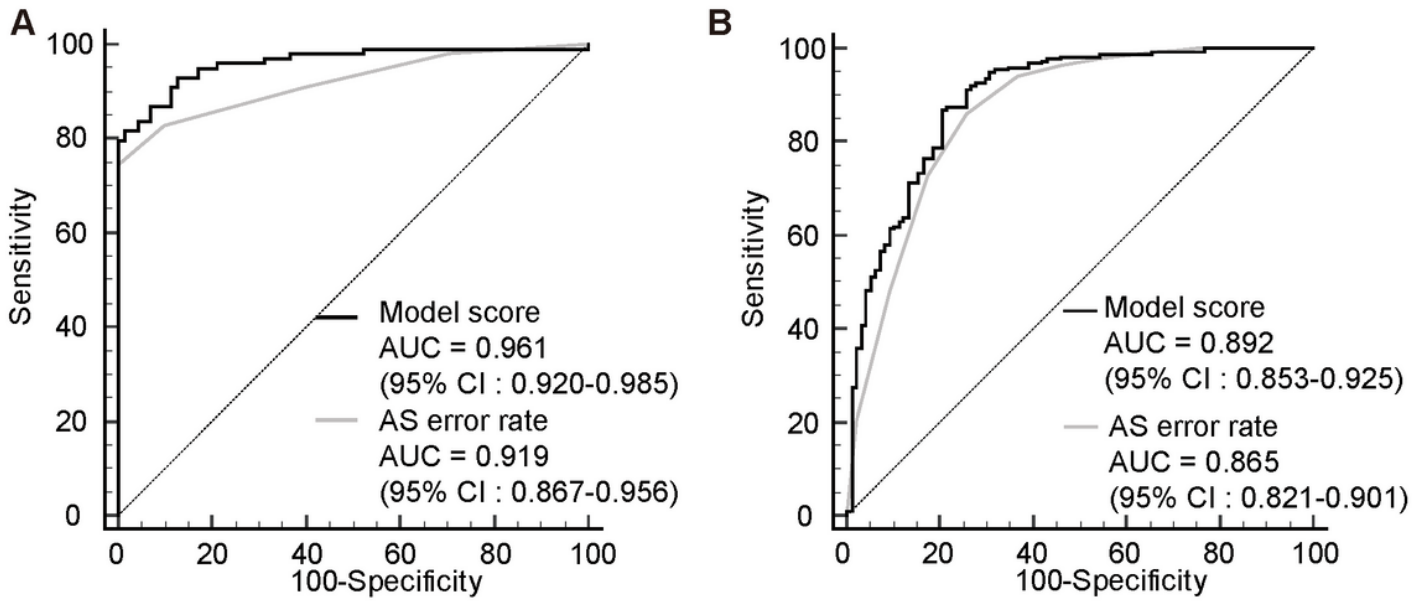

Figure 7

Comparison of diagnostic performance between saccade measurements and MMSE scores. (**A**) ROC curve analysis of the diagnostic performance by measuring saccades (model score) and by MMSE test for discriminating patients with cognitive impairment (MCI + dementia) from the EHC group. (**B**) ROC curve analysis of diagnostic performance by measuring saccades (model score) and by the MMSE test for discriminating patients with cognitive impairment (MCI + dementia) from the remaining three groups (EHC + ESHC + SMCI).