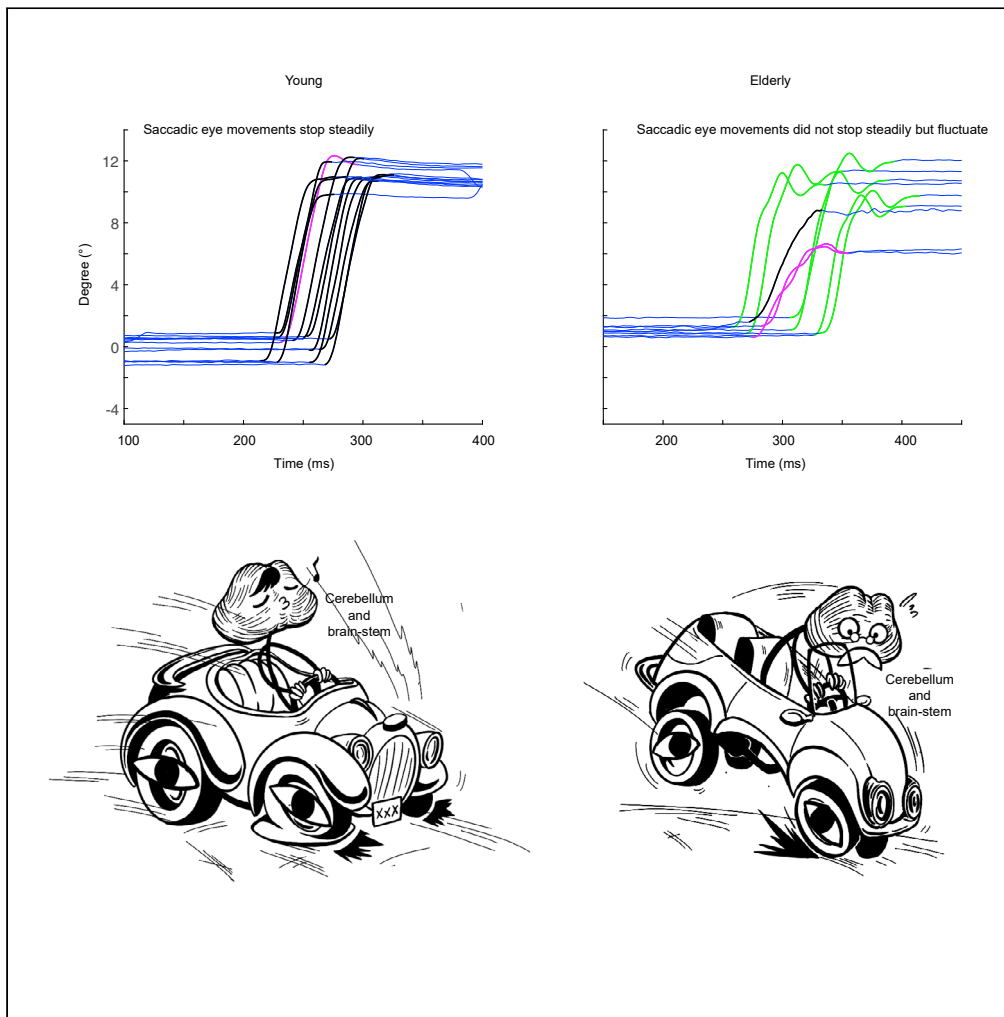


Article

Spatiotemporal characteristics of postsaccadic dynamic overshoot in young and elderly subjects



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Highlights

We classify two types of saccadic dynamic overshoot (SDO): SDO_{simple} and SDO_{complex}

Saccades with SDO have higher peak velocity and deceleration than saccades without SDO

Elderly subjects show a higher frequency and amplitude of SDO than young subjects

Saccades with SDO_{complex} occur more frequently in reflexive than voluntary saccades

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Article

Spatiotemporal characteristics of postsaccadic dynamic overshoot in young and elderly subjects

Min Li,¹ Junru Wu,¹ Wenbo Ma,¹ Zhihao Zhang,¹ Mingsha Zhang,¹ Xuemei Li,^{2,*} Zhipei Ling,^{3,*} and Xin Xu^{3,4,*}

SUMMARY

Saccadic eye movements may not stop steadily but fluctuate briefly, known as saccadic dynamic overshoot (SDO). The reported relationships between SDO and saccadic parameters of main saccade and the effect of aging on SDO are controversial. In addition, it is not clear whether aging-related disease, such as mild cognitive impairment (MCI) and Parkinson disease (PD), causes the specific change of SDO. To address these questions, we analyzed the spatiotemporal features of SDO in young healthy subjects, elderly healthy subjects, and subjects with PD and MCI in three oculomotor tasks. We found two types of SDOs—simple and complex SDO. We confirmed that the frequency and amplitude of SDO were positively correlated with the peak velocity and deceleration of main saccades and increased in elderly subjects; however, they were not significantly different among the three elderly groups. Our results support the previous argument that the oculomotor structure in brainstem and cerebellum directly develop SDO.

INTRODUCTION

Saccades are ballistic eye movements that quickly rotate the eyes to direct the center of the retina, i.e., the fovea, to attractive objects in the visual field. Primates perform two to three saccades per second on average to help the visual system collecting high-acuity visual information (Robinson, 1964). Despite the high demand of the visual system for saccades to be highly accurate, saccades do not always end precisely, e.g., saccades may not stop fully at the desired fixation point but continue to fluctuate after the main saccades. Post-saccadic instability exhibits a number of spatiotemporal profiles in both eye position and saccadic velocity, which has been referred to as saccadic dynamic overshoot (SDO), saccadic dynamic undershoot, and saccadic glissades (Enderle, 2002; Mardanbegi et al., 2018; Nystrom et al., 2013; Van Gisbergen et al., 1981). Among them, SDO is the most common type (Bahill et al., 1975b) and represents the subject of the present study.

SDO has been identified in humans (Bahill et al., 1975b; Cogan, 1954; Kapoula et al., 1986; Mardanbegi et al., 2018) and nonhuman primates (Fuchs, 1967; Kimmel et al., 2012; Van Gisbergen et al., 1981) by various eye-tracking techniques, including magnetic scleral search coils (Deubel and Bridgeman, 1995a; Fuchs, 1967; Kapoula et al., 1986; Kimmel et al., 2012; Van Gisbergen et al., 1981), electrooculography (Schiller, 1970), video-based limbus tracking systems (Bahill et al., 1975b; Zuber et al., 1965), video-based pupil tracking systems (Kimmel et al., 2012; Mardanbegi et al., 2018; Nystrom et al., 2013), and video-based Purkinje image (reflexes) systems (Kimmel et al., 2012; Mardanbegi et al., 2018; Nystrom et al., 2013). However, the video-based eye tracking systems detect the most vigorous SDO signal compared with the other systems (Choe et al., 2016; Deubel and Bridgeman, 1995a, 1995b; Kimmel et al., 2012; Mardanbegi et al., 2018; McCamy et al., 2015; Nystrom et al., 2016; Nystrom et al., 2013; Schmitt et al., 2007; Traisk et al., 2005). One reason is that, for the video-based limbus tracking and pupil tracking systems, the acceleration and deceleration of saccades are very quick, which can reach over $20,000^{\circ}/s^2$ for a 10° saccade (Bahill et al., 1981). During the acceleration phase of saccade, the lens lags behind the rest of the eyeball. Then during the deceleration phase, the lens movement is slowed by the elastic zonules. Therefore, after the eyeball stops rotation during a saccade, the lens still moves along the direction of saccade and overshoots the final position of eyeball and is pulled back by passive elastic forces of the zonules (Deubel and Bridgeman, 1995a, b). Another reason is that, for the video-based Purkinje image systems, the relative movement of the iris related to the center of pupil at the end of saccade causes the post-saccadic instability (Nystrom et al., 2013). Therefore, these studies argued that the SDO reflected the local motion of the lens and iris in relation to the rest of the eyeball. However, the discovery of SDO by utilizing various eye-tracking

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techniques reveals that, in addition to the local motion of the lens and iris, SDO also reflects the instability of eyeball rotations at the end of saccades. A previous computational modeling study also argued that the SDO cannot be attributed to the biomechanical properties of the eye movement mechanisms but was caused by the variation in neural control of saccades (Bahill et al., 1975a).

The frequency of SDO is quite capricious in individual subjects, i.e., SDO can occur on one day but is almost absent on another day (Bahill et al., 1975b). The reported frequency of SDO varies from 5% to 70% depending on the subject and experimental setup (Bahill et al., 1975b; Kapoula et al., 1986; Kimmel et al., 2012; Lehman and Stark, 1983). Reports have indicated that the frequency and amplitude of SDO in an individual subject are positively correlated with the velocity and deceleration of main saccades, i.e., a higher velocity and deceleration in main saccades corresponds to a greater number and amplitude of SDO (Hooge et al., 2015; Kimmel et al., 2012; Mardanbegi et al., 2018). However, controversial findings have also been reported (Deubel and Bridgeman, 1995a; Fuchs, 1967; Kimmel et al., 2012) (Hooge et al., 2015; Kapoula et al., 1986; Van Gisbergen et al., 1981). So, the first goal of the present study is to determine the parameters of main saccade that are highly correlated with the occurrence of SDO, which will help to address the inconsistent and controversial findings among previous studies and to understand the possible mechanisms underlying SDO generation. Based on the common knowledge that it is more difficult to steadily stop a fast-moving object, we hypothesize that saccades with higher peak velocity and deceleration are more likely to have SDO. If our hypothesis is true, the occurrence of SDO should be different between young and elderly subjects, because the peak velocity of saccades is different between them (Dowiasch et al., 2015; Irving et al., 2006; Sharpe and Zackon, 1987; Spooner et al., 1980; Warabi et al., 1984). Indeed, previous studies have found that the amplitude of SDO was correlated with the subjects' age, but these studies showed opposite results. One paper illustrated that the amplitude of SDO increased in elderly subjects (Mardanbegi et al., 2018), whereas another paper showed that the amplitude of SDO decreased in elderly subjects (Deubel and Bridgeman, 1995a). The second goal of the present study is to approach the aging effect on SDO.

Several studies note that saccadic accuracy relies highly on the function of lower oculomotor structures (saccadic generator) in the brainstem and cerebellum (Optican and Pretegianni, 2017; Van Gisbergen et al., 1981; Zee and Robinson, 1979); so far researches on the neural mechanisms underlying SDO have mainly focused on investigating the role of these oculomotor structures (Bahill et al., 1975a, b; Ramat et al., 2005; Ramat et al., 2008; Shaikh et al., 2008). As we know, there are other oculomotor structures in the brain, e.g., the cerebral cortex, basal ganglia, and superior colliculus, which play important roles in the control of saccades. However, the effects of these higher oculomotor structures on SDO have not been explored. Therefore, the third goal of the present study is to assess the role of higher oculomotor structures in the development of SDO. Our hypothesis is that, if the higher oculomotor structures have the function to develop SDO as the lower oculomotor structures do, the specific changes in the spatiotemporal properties of SDO are expected to be seen in patients with PD and MCI compared with elderly healthy subjects. Otherwise, if the higher oculomotor structures just serve as a modulator to affect SDO through modulating the activity of lower oculomotor structures, there are no specific changes of SDO in patients with PD and MCI compared with elderly healthy subjects.

In the present study, we analyzed the spatiotemporal characteristics of SDO in four groups of human subjects, namely, young healthy subjects, elderly healthy subjects, and patients with PD and MCI and in three saccadic tasks, i.e., visually guided step saccade, anti-saccade, and memory-guided saccade tasks (Figure S1). According to our data analysis criteria, we found two types of SDOs that show varied spatiotemporal properties: the simple saccadic dynamic overshoot (SDO_{simple}) with one backward small saccade immediately following the main saccade and the complex saccadic dynamic overshoot (SDO_{complex}) with one backward and one forward small saccade immediately following the main saccade (Figure S2). We intend to address the following questions: (1) what parameters of the main saccade are highly correlated with the occurrence of SDO? (2) what is the effect of aging on SDO? (3) would the impairments of oculomotor structures in PD and MCI cause the specific changes of SDO?

RESULTS

Saccadic main sequence analysis shows that SDOs are small saccades

SDOs were identified as saccadic eye movements in our analysis (see methods for details). We analyzed the correlation between saccadic amplitude and peak velocity of all main saccades and their

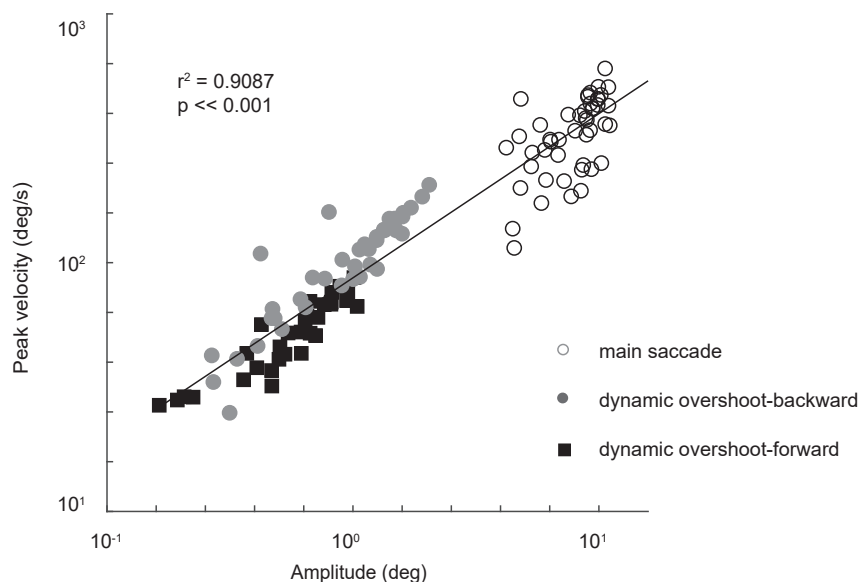


Figure 1. Results of the main sequence analysis included main saccades and adhered SDO

adhered SDOs, i.e., the saccadic main sequence analysis. We performed the linear regression on the log-transformed values of saccadic amplitude and peak velocity for each individual subject. The result of an example subject is plotted in Figure 1, which shows that the majority of data points, including the main saccades, SDO backward saccades, and SDO forward saccades, are linearly distributed in the log-log scale (linear regression, $r^2 = 0.909$, $p \ll 0.001$). Indeed, all subjects have such linear correlation between saccadic amplitude and peak velocity in the log-log scale ($r^2 = 0.911$ on average, with a standard deviation of 0.081). These results indicate that the SDOs are indeed small saccadic eye movements.

Frequency and amplitude of SDO are higher in elderly subjects than in young subjects but not significantly different among the three groups of elderly subjects

The effect of aging on the frequency and amplitude of SDO was disputed among previous studies (Deubel and Bridgeman, 1995a; Mardanbegi et al., 2018). In addition, whether and how neurodegenerative diseases, such as PD and MCI, cause specific changes in the frequency and amplitude of SDO are unknown. To approach these questions, we calculate the fractions of SDO for each subject in each task and compare them among the four different groups of subjects. As shown in Figure 2A, the three groups of elderly subjects had a greater fraction of SDO than the young subjects in all three tasks. The difference is significant in the anti-saccade and memory-guided saccade tasks (Kruskal-Wallis test, anti-saccade, $p < 0.001$; memory-guided saccade, $p < 0.001$, Bonferroni correction, $\alpha = 0.05/6$), although it does not reach the significant level in the visually guided step saccade task (Kruskal-Wallis test, $p = 0.074$). However, significant differences were not observed among the three groups of elderly subjects in any task (Tukey-Kramer multiple comparison test, all p values > 0.900).

Furthermore, we also calculated the fraction of SDO_{complex} over all SDOs. The results show that the average fractions of SDO_{complex} in the young subjects were significantly lower than those in the elderly subjects (by over 20%) in all three tasks (Figure 2B; Kruskal-Wallis test, visually guided step saccade, $p = 0.004$; anti-saccade, $p < 0.001$; memory-guided saccade, $p = 0.002$, Bonferroni correction, $\alpha = 0.05/6$). However, there were no significant differences among the three elderly groups in any task (Tukey-Kramer multiple comparison test, all p values > 0.541). Such results indicate that, although young subjects have a considerable fraction of saccades with SDOs, the majority of SDOs are the simple type, whereas elderly subjects have a greater fraction of saccades with SDOs than young subjects and approximately half of the SDOs are the complex type.

We also compared the amplitude of the first return phase of SDOs (amplitude of SDO) among the four groups of subjects (Figure 2C). Overall, the average amplitude of SDO is smaller in the young subjects

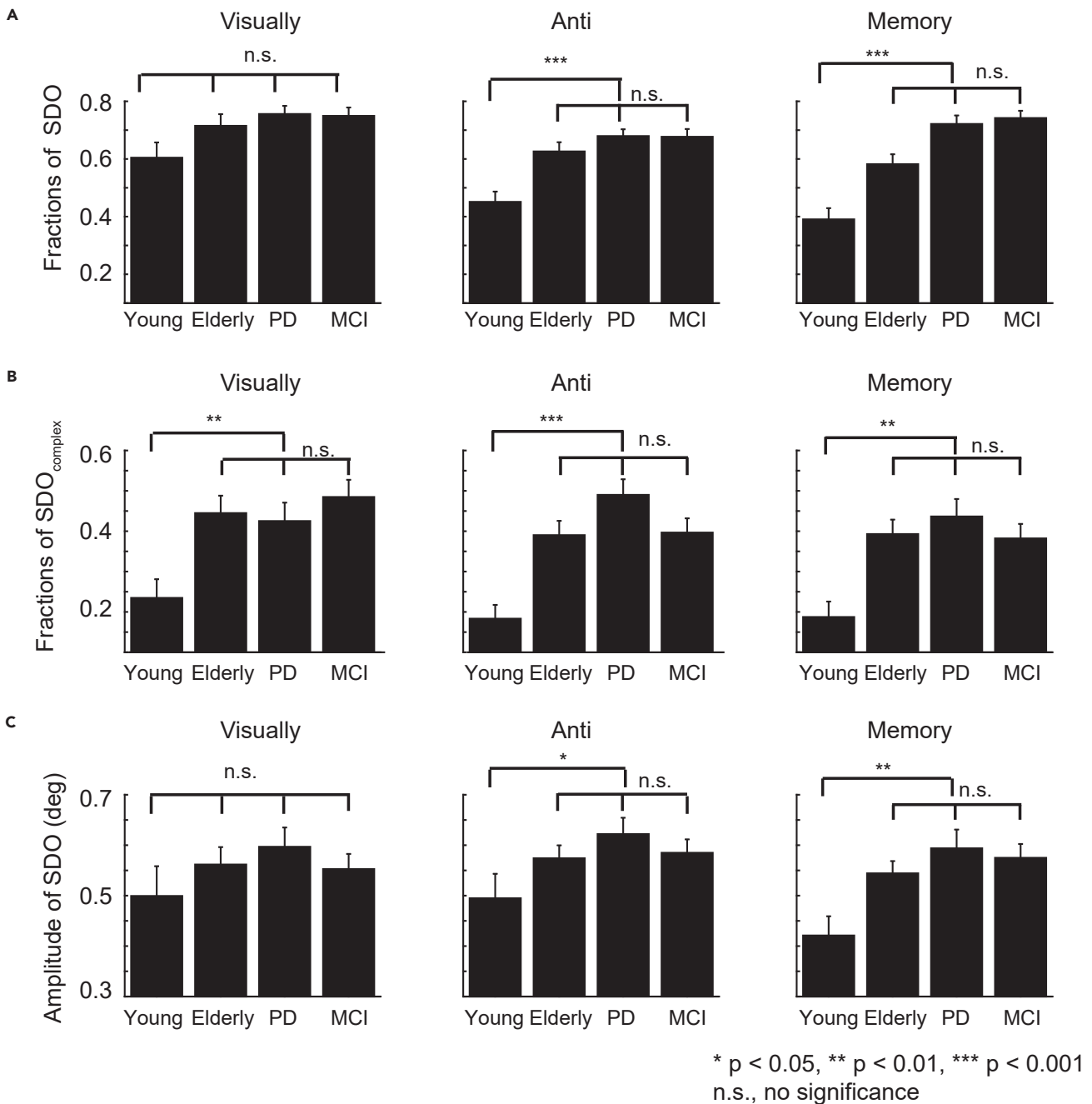


Figure 2. Frequency and amplitude of SDO in three tasks

(A) Average fraction of SDO for four groups of subjects performing three tasks.

(B) Similar to A but for the proportion of $SDO_{complex}$.

(C) Similar to A but for the amplitude of the first return phase of SDO. Error bars, standard error of mean.

than in the elderly subjects in all three tasks. In particular, the difference is significant in both anti-saccades and memory-guided saccades (Kruskal-Wallis test, $p = 0.018$ and $p = 0.005$, respectively, Bonferroni correction, $\alpha = 0.05/6$), although it does not reach significant level in the visually guided step saccade task (Kruskal-Wallis test, $p = 0.177$). Again, significant differences were not observed among the three groups of elderly subjects in any task (Tukey-Kramer multiple comparison test, all p values > 0.10).

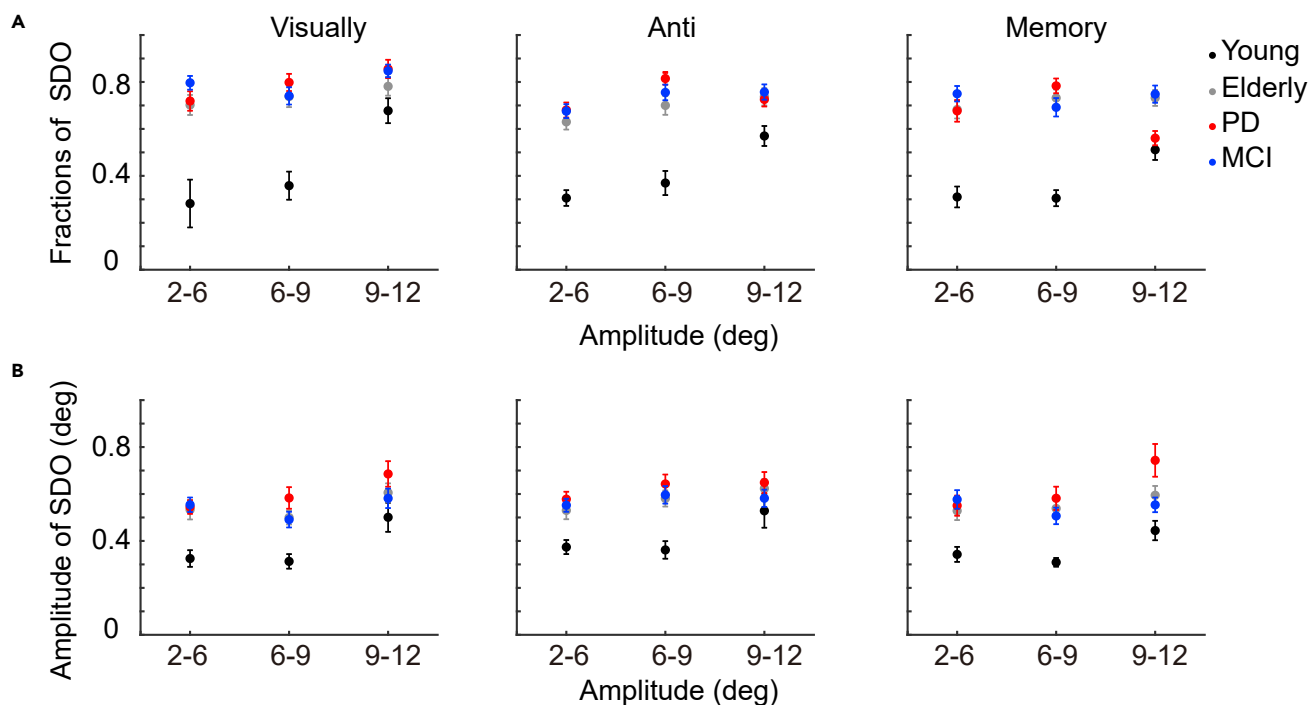


Figure 3. Correlation of the frequency and amplitude of SDO with the amplitude of main saccades

Top, correlation between the frequency of SDO and the amplitude of main saccades. Bottom, similar to the top but for the amplitude of SDO. Error bars, standard error of mean.

Young subjects but not elderly subjects showed greater frequency and amplitude of SDO in saccades with larger amplitude than with smaller amplitude

The relationship between the frequency/amplitude of SDO and the amplitude of the main saccades is controversial among previous studies. Here, we group the main saccades into three subsets based on the saccadic amplitude (2–6°, 6–9°, and 9–12°). For each individual subject, the required minimum trial number in each subset is five. Our data show that, in the young subjects, the frequency (Figure 3A) and amplitude (Figure 3B) of SDO are greater in saccades with larger amplitudes (>9°) than in saccades with smaller amplitudes (<9°) (Kruskal-Wallis test with Tukey-Kramer multiple comparison test, frequency: visually guided step saccade, $p = 0.010$; anti-saccade, $p = 0.009$; memory-guided saccade, $p = 0.007$; amplitude: visually guided step saccade, $p = 0.032$; anti-saccade, $p = 0.079$; memory-guided saccade, $p = 0.012$, Bonferroni correction, $\alpha = 0.05/3$). In contrast, significant differences were not observed in the three groups of elderly subjects (all p values > 0.152) (Figures 3A and 3B). Such results show that, in elderly subjects, the amplitude of the main saccade is not closely correlated with the occurrence of SDO.

Saccades with SDO have higher peak velocity and deceleration than saccades without SDO

If saccadic amplitude is not highly correlated with the frequency of SDO in elderly subjects, what factors might be? An intuitive thought is that, among saccades with similar amplitude, some of them with SDO might have higher velocity and/or deceleration, because in this case it is more difficult to brake the eye at the end of a saccade. To examine this speculation, both peak velocity and deceleration of main saccades were compared among the four groups of subjects based on the SDO characteristics (SDO_{without} , SDO_{simple} , and SDO_{complex}). In order to avoid any potential effect of saccadic amplitude on peak velocity and deceleration, the main saccades of each subject are grouped into three subsets according to the main saccadic amplitude (2–6°, 6–9°, and 9–12°). As shown in Figure 4A, all four groups of subjects show that, in all three tasks, SDO_{complex} has the highest peak velocity and SDO_{simple} has a higher peak velocity than SDO_{without} (Kruskal-Wallis test, visually guided step saccade, p values < 0.05 except 2–6° in the young group; anti-saccade, p values < 0.01; memory-guided saccade, p values < 0.05). Although these results clearly show that saccades with SDO have higher peak velocities than those without SDO, an obvious boundary is not available to separate saccades with SDO from saccades without SDO throughout the three subsets of data.

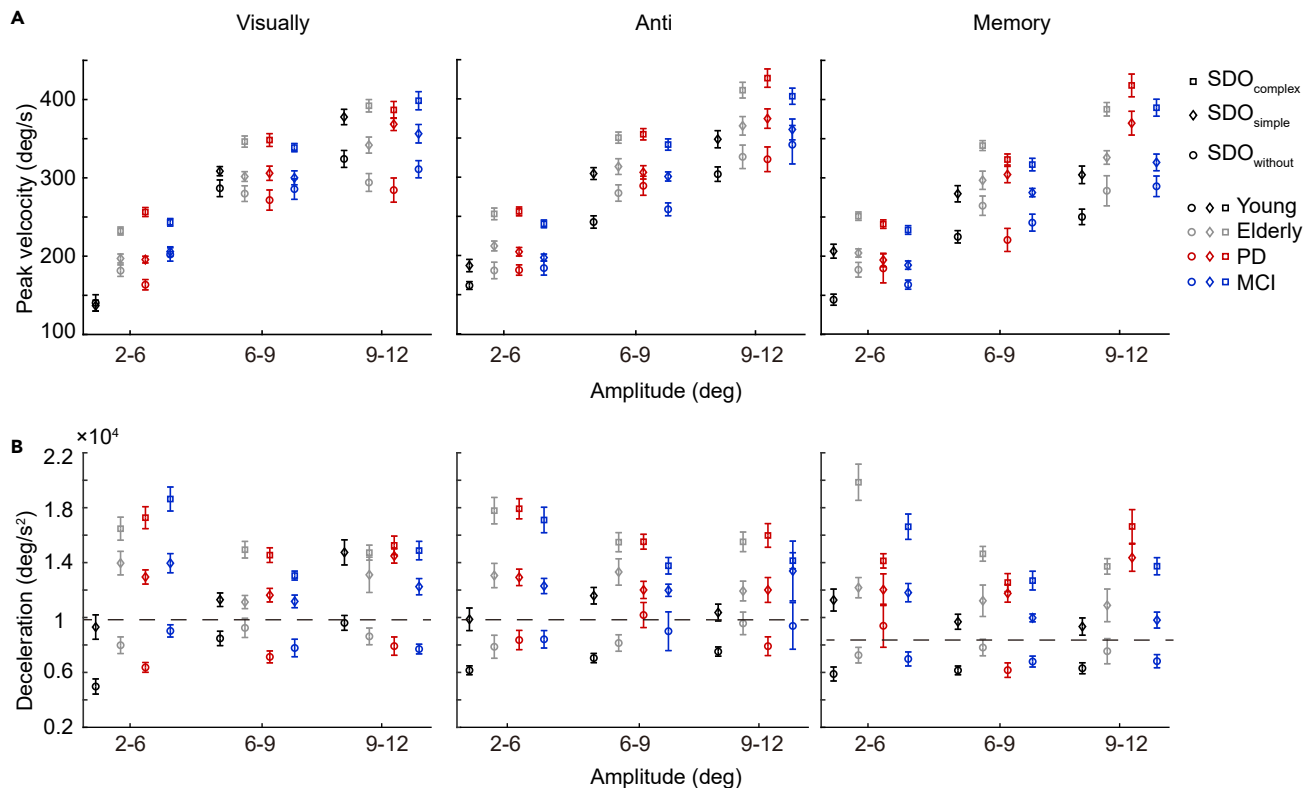


Figure 4. Comparison of peak velocity and deceleration among different types of main saccades with comparable saccadic amplitude

(A) Comparison of saccadic peak velocity among three types of saccades (SDO_{without}, SDO_{simple}, and SDO_{complex}; different shapes of symbols). (B) Similar to A but for saccadic deceleration. Error bars, standard error of mean.

Then, we analyzed the data of deceleration by applying a similar method as the peak velocity analysis. All four groups of subjects in the three tasks show that SDO_{complex} has the highest saccadic deceleration and SDO_{simple} has higher saccadic deceleration than SDO_{without} (Figure 4B, Kruskal-Wallis test, visually guided step saccade, p values < 0.05 except 2–6° in the young group; anti-saccade, p values < 0.05 ; memory-guided saccade, p values < 0.05). Moreover, a boundary (horizontal dashed line) denoting the 85% probability of the occurrence of SDO could be found in all three tasks.

Frequency and amplitude of the SDO positively correlate with the peak velocity and deceleration of the main saccades

We further analyzed the correlation between the peak velocity and the frequency/amplitude of the SDO. As shown in Figure 5A, the frequency and amplitude of SDO are positively correlated with the saccadic peak velocity in all four groups of subjects and three tasks (r values > 0.80). Not surprisingly, a similar positive correlation was also observed between saccadic deceleration and the frequency/amplitude of SDO (Figure 5B).

Results in Figures 4 and 5 indicate that the saccadic peak velocity and deceleration are more closely correlated with the occurrence of SDO than the saccadic amplitude, which supports our working hypothesis that the occurrence of SDO might be closely correlated with the peak velocity and deceleration of main saccade and saccades with dynamic overshoot have higher peak velocity and deceleration than saccades without dynamic overshoot.

The deceleration of main saccades is higher in elderly subjects than in young subjects

We have demonstrated that the elderly subjects have more fraction of SDO than young subjects (Figure 2), and saccades with SDO have a higher peak velocity and deceleration than saccades without SDO (Figures 4 and 5). Based on these results, we propose that the peak velocity and mean deceleration of main saccades are different between young and elderly subjects. To test this theory, for each group of subjects, we

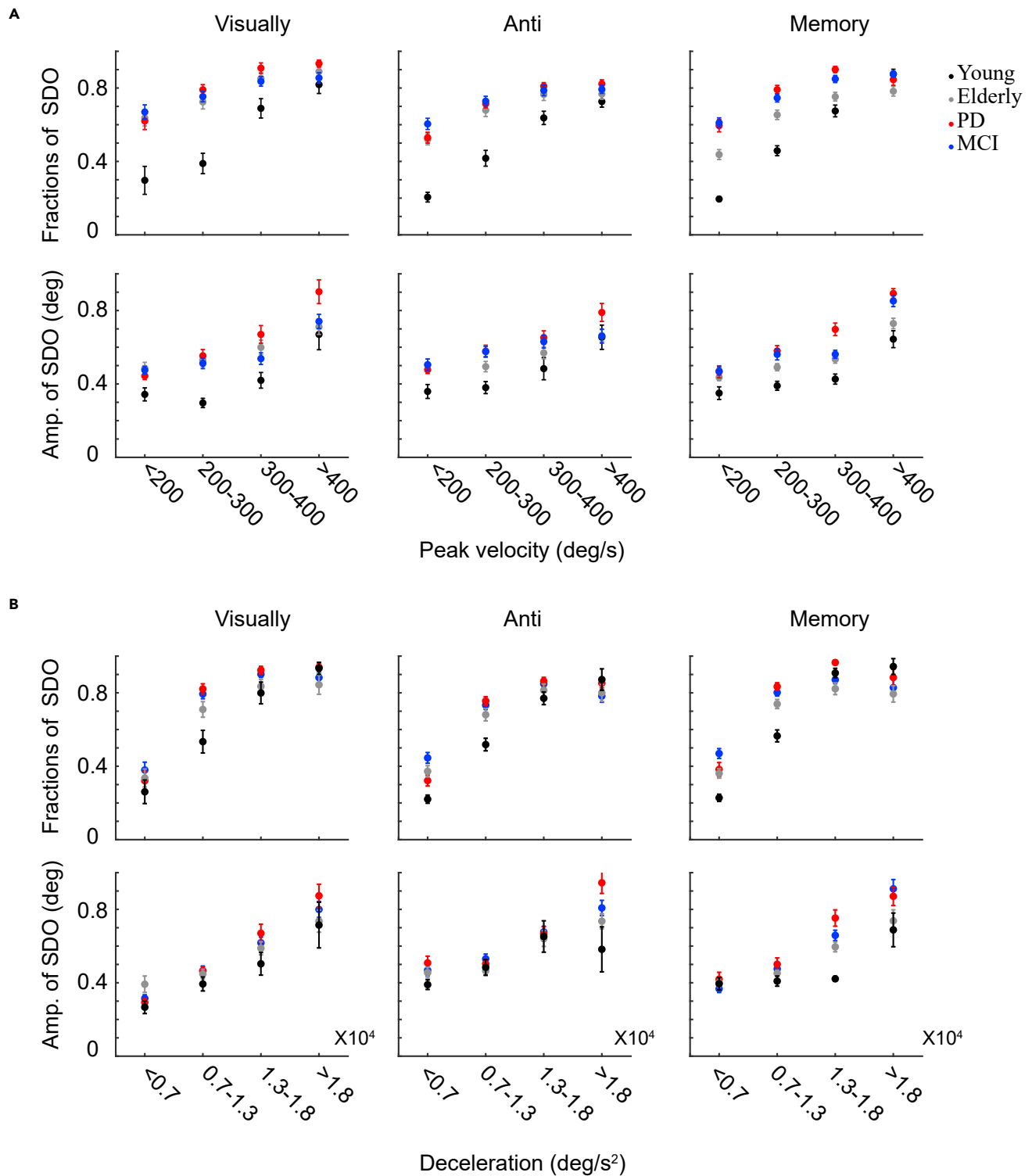


Figure 5. Correlation of the frequency and amplitude of SDO with peak velocity and deceleration

Correlation of the frequency (top rows) and amplitude (bottom rows) of SDO with saccadic peak velocity (A) and deceleration (B). Error bars, standard error of mean.

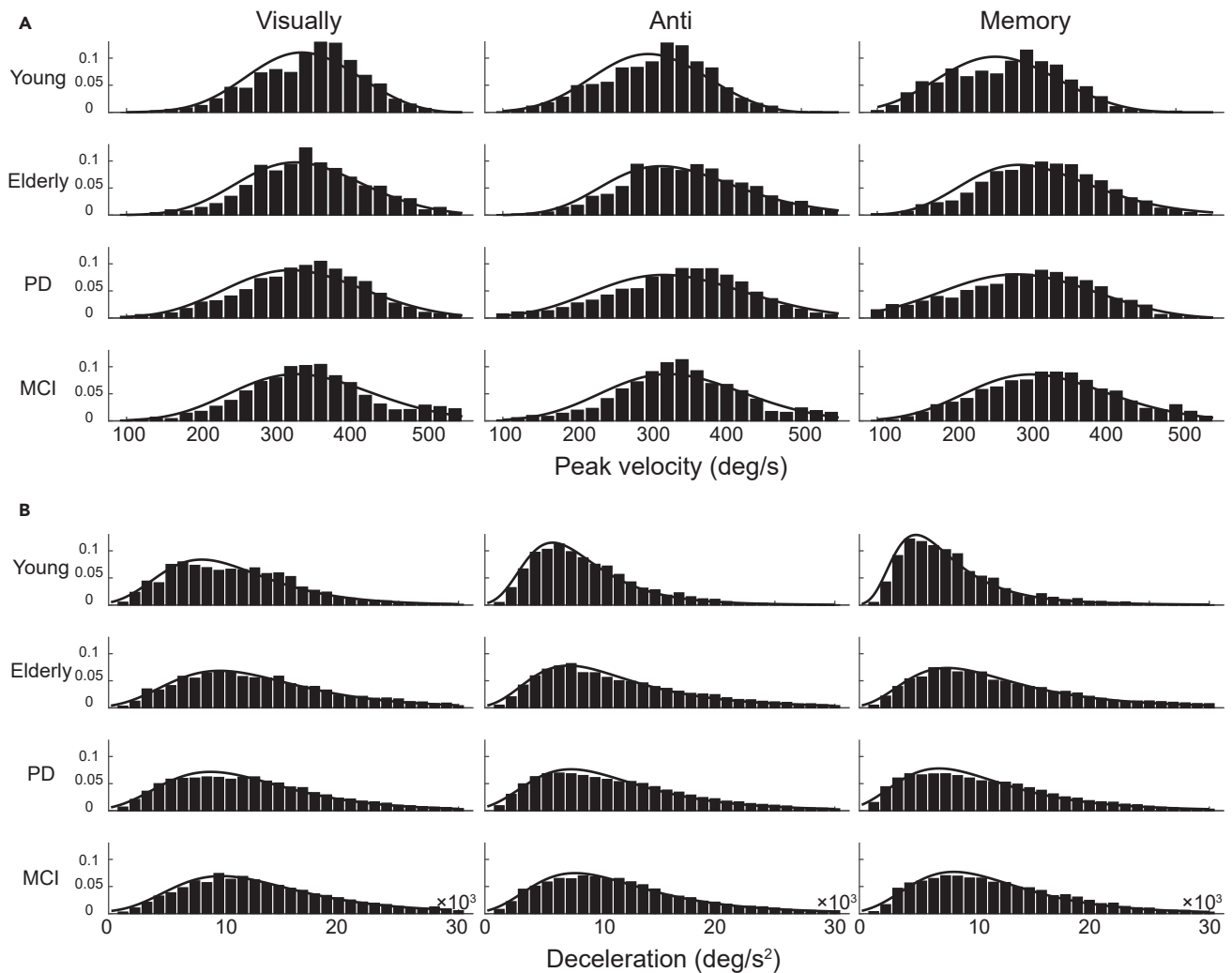


Figure 6. Peak velocity and deceleration distribution with generalized extreme value probability distribution fitting in four groups of subjects and in three tasks

The histograms represent the probability density distribution of different groups of subjects, and the curves represent the generalized extreme value probability distribution fitting for relevant distribution, respectively.

calculate the distribution of peak velocity and mean deceleration of main saccades. For peak velocity analysis, we only include trials whose saccadic amplitude is between 7° and 11°. The results are shown in Figure 6, in which the histograms with generalized extreme value probability distribution fitting represent the distributions of peak velocity (Figure 6A) and mean deceleration (Figure 6B), respectively. The medians of peak velocity and mean deceleration distributions of four groups of subjects are presented in Table 1. The statistical analysis shows that the peak velocity distributions are similar among four groups of subjects in three tasks (Kruskal-Wallis test, all $p > 0.873$, Bonferroni correction, $\alpha = 0.05/6$), whereas the medians of mean deceleration distribution are smaller in young subjects than in elderly subjects in three tasks. Moreover, the mean deceleration distribution of young subjects is significantly smaller than elderly subjects in anti-saccade and memory-guided saccade tasks (Kruskal-Wallis test, all $p < 0.001$ and all $p < 0.001$, respectively, Bonferroni correction, $\alpha = 0.05/6$), whereas the difference does not reach statically different level in visually guided step saccade task (Kruskal-Wallis test all $p > 0.767$ Bonferroni correction, $\alpha = 0.05/6$). Also, there are no significant differences among the three elderly groups in any task (Tukey-Kramer multiple comparison test, all $p > 0.813$, Bonferroni correction, $\alpha = 0.05/6$). Such results indicate that the higher frequency of SDO in elderly subjects is correlated with the higher deceleration compared with young subjects.

Table 1. Medians of peak velocity and deceleration of four group subjects in three tasks

Task	Subject group	PV median	Deceleration median
Visually guided step saccade	Young	344.37	10.43
	Elderly	333.96	12.22
	PD	332.35	11.44
	MCI	335.03	12.41
Anti-saccade	Young	304.70	7.86
	Elderly	335.35	10.29
	PD	334.57	10.30
	MCI	328.76	10.86
Memory-guided saccade	Young	270.35	7.11
	Elderly	312.68	10.67
	PD	294.93	9.80
	MCI	321.30	10.77

PV, peak velocity; Young, young healthy subjects; Elderly, elderly healthy subjects; PD, subjects with Parkinson disease; MCI, subjects with mild cognitive impairment.

SDO_{complex} occurs more frequently in reflexive saccades than in voluntary saccades

To investigate the effects of higher oculomotor structures on the spatiotemporal properties of SDO, we compared the SDOs between reflexive and voluntary saccades because the performance of voluntary saccades requires the involvement of higher oculomotor structures in neocortex and basal ganglia. The definitions of reflexive and voluntary saccades in the present study are the following: reflexive, corrective saccades in visually guided step saccades, and certain error trials in anti-saccade and memory-guided saccade, see [Figure S1](#); and voluntary saccades, corrective saccades in anti-saccades and memory-guided saccades, see [Figure S1](#). Elderly subjects frequently made reflexive saccades toward the visual target immediately after its appearance in both the anti-saccade and memory-guided saccade tasks. We were able to compare the probability of SDO occurrence between reflexive saccades and voluntary saccades within each of these two tasks in the elderly groups. However, the young subjects made very few reflexive saccades in either anti-saccade or memory-guided saccade tasks. Thus, we compared the occurrence of SDO between reflexive and voluntary saccades across all three tasks.

As shown in [Figure 7A](#), the fraction of SDO_{complex} is significantly higher in reflexive saccades than in voluntary saccades in both tasks for all three groups of elderly subjects (Wilcoxon signed rank test, anti-saccades: elderly healthy, $p < 0.001$; PD, $p < 0.001$; MCI, $p < 0.001$; memory-guided saccades: elderly healthy, $p < 0.001$; PD, $p < 0.001$; MCI, $p < 0.001$). In contrast, the fraction of SDO_{simple} is not significantly different between reflexive and voluntary saccades (Wilcoxon signed rank test, anti-saccades: elderly healthy, $p = 0.187$; PD, $p = 0.327$; MCI, $p = 0.367$; memory-guided saccades: elderly healthy, $p = 0.964$; PD, $p = 0.236$; MCI, $p = 0.037$). What might cause the differences between reflexive and voluntary saccades? To address this question, we compare the peak velocity and deceleration between reflexive and voluntary saccades in the following analysis.

For all three elderly subjects, the peak velocity and deceleration in reflexive saccades are significantly higher than those in voluntary saccades in both anti-saccade and memory-guided saccade tasks (Wilcoxon signed rank test). The test results are as following: peak velocity: anti-saccades, $p = 0.070$, $p = 0.0008$, $p = 0.040$; memory-guided saccades, $p = 0.013$, $p = 0.033$, $p = 0.020$; deceleration: anti-saccades, $p \ll 0.001$, $p \ll 0.001$, $p \ll 0.001$; memory-guided saccades, $p \ll 0.001$, $p \ll 0.001$, $p \ll 0.001$ for the elderly healthy, PD, and MCI, respectively ([Figure 7B](#)). For the young subjects, the fraction of SDO_{complex} was higher in the visually guided step saccade task than the anti-saccade task (Wilcoxon signed rank test, $p = 0.044$) and in the memory-guided saccade task (Wilcoxon signed rank test, $p = 0.018$). The fraction of SDO_{simple} was significantly higher in the visually guided step saccade task than in the memory-guided saccade task (Wilcoxon signed rank test, $p = 0.011$) but not in the anti-saccade task (Wilcoxon signed rank test, $p = 0.324$) ([Figure 7C](#)). In addition, the peak velocity and deceleration were greater in the visually guided step saccade task than in the anti-saccade task (Wilcoxon signed rank test, $p < 0.001$) and memory-guided saccade task (Wilcoxon signed rank test, $p < 0.001$), respectively ([Figure 7D](#)).

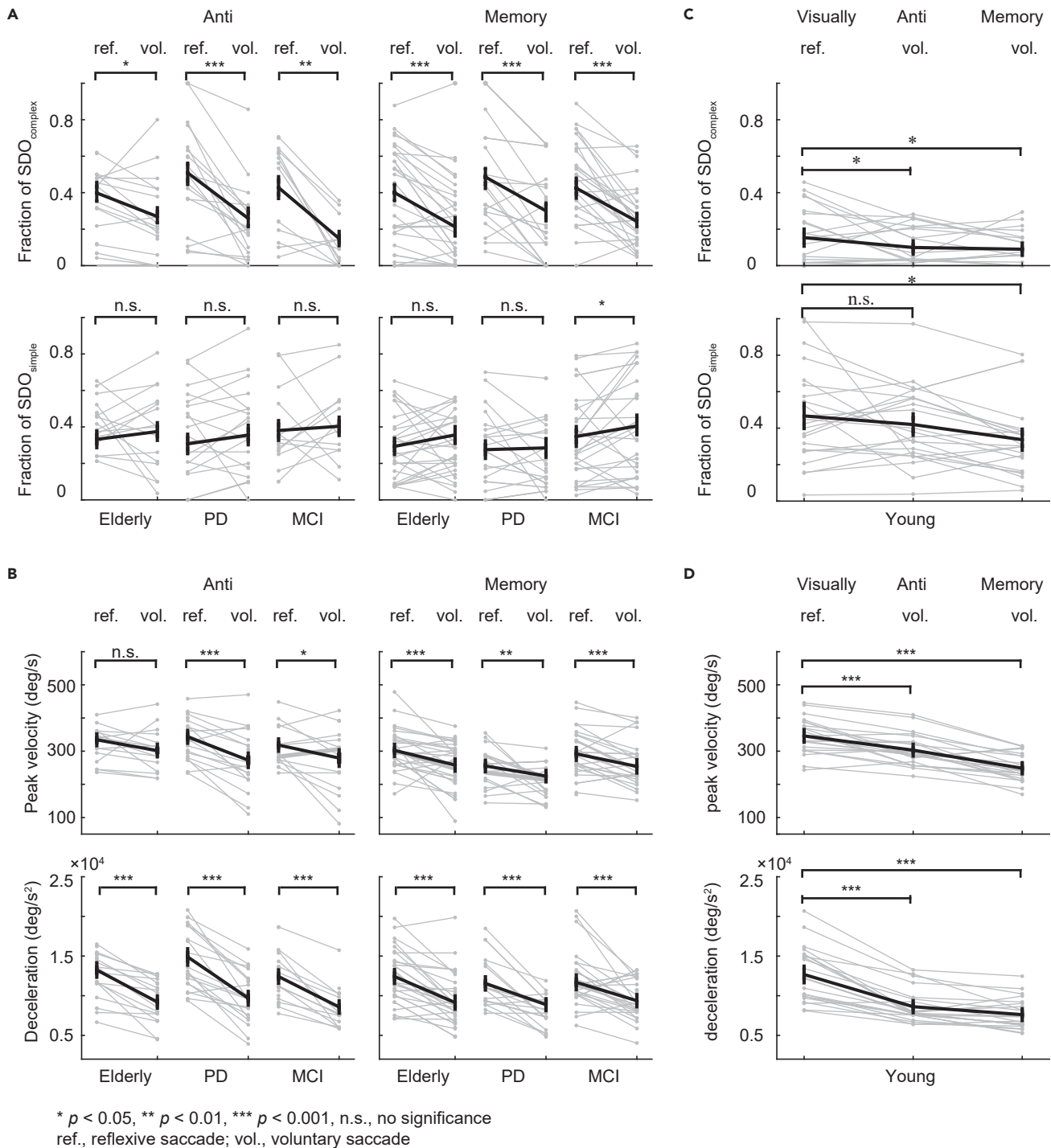


Figure 7. Comparison of the SDO frequency between reflexive and voluntary saccades

(A) Comparison of the fraction of SDO (top, SDO_{complex}; bottom, SDO_{simple}) between reflexive (ref.) and voluntary (vol.) saccades for three groups of elderly subjects performing anti-saccade (anti) and memory-guided saccade (memory) tasks.

(B) Similar to A but for saccadic peak velocity and deceleration.

(C) Comparison of the fraction of SDO (top, SDO_{complex}; bottom, SDO_{simple}) between reflexive (from visually guided step saccade task) and voluntary (from anti-saccade and memory-guided saccade task) saccades in young subjects.

(D) Similar to C but for the saccadic peak velocity and deceleration. Error bars, standard error of mean.

Such results indicate that the reduction of SDO in voluntary saccades compared with reflexive saccades might be due to the modulation of the higher oculomotor structures on the lower oculomotor structures, which decreases the saccadic peak velocity and deceleration.

DISCUSSION

We proposed two hypotheses regarding the possible mechanisms underlying the occurrence of SDO. Our first working hypothesis is that the occurrence of SDO might be closely correlated with the peak velocity and deceleration of the main saccade. The second working hypothesis is that, if the higher oculomotor structures have the function to develop SDO as the lower oculomotor structures do, the specific changes in the spatiotemporal properties of SDO are expected to be seen in patients with PD and MCI compared with elderly healthy subjects. To test these hypotheses, we analyzed the spatiotemporal characteristics of SDO in four groups of human subjects, namely, young subjects, elderly healthy subjects, and patients with PD and MCI, while they were performing three saccadic tasks (visually guided step saccade, anti-saccade, and memory-guided saccade). According to our velocity dual-threshold criteria, we found two types of SDOs, i.e., simple saccadic dynamic overshoot (SDO_{simple}) and complex saccadic dynamic overshoot (SDO_{complex}). The frequency and amplitude of SDO, in particular of SDO_{complex}, was significantly higher in the elderly subjects than in the young subjects. Young subjects but not elderly subjects showed greater frequency and amplitude of SDO in saccades with larger amplitude than with smaller amplitude. On the other hand, for both young and elderly subjects, main saccades with similar amplitudes showed greater peak velocity and deceleration with SDO_{complex} than with SDO_{simple} and greater peak velocity and deceleration with SDO_{simple} than with SDO_{without}. Across the three tasks, the decelerations of main saccades are greater in elderly subjects than in young subjects. In addition, regardless of the saccadic amplitude, the probability of SDO occurrence positively correlates with the peak velocity and deceleration of the main saccades. Moreover, for the four groups of subjects in each task, we are able to find a deceleration boundary to separate main saccades with SDO from those without SDO. Finally, the frequency and amplitude of SDO are smaller in voluntary saccades than in reflexive saccades, which is probably due to lower peak velocity and deceleration in voluntary saccades.

Although these results fully support our working hypotheses, they also allow us to make the following assumption regarding the possible neural mechanisms underlying SDO generation. First, considering the fact that the pathological impairments of PD and MCI are mainly in the basal ganglia and neocortex, respectively, the similar occurrence of SDO among elderly healthy control and subjects with PD and MCI suggests that the higher oculomotor structures in basal ganglia and neocortex do not directly develop SDO. Second, considering the involvement of higher oculomotor structure in performing of voluntary saccades, the decrease of SDO in anti-saccades and memory-guided saccades suggests that the higher oculomotor structures could affect the occurrence of SDO through modifying the activity of lower oculomotor structures, which alters the velocity and deceleration of main saccades.

Frequency and amplitude of SDO in the present study are consistent with previous reports

The frequency of SDO can be quite arbitrary in individual subjects from day to day (Bahill et al., 1975b). The reported frequency of SDO also varies from 5% to 70% among previous studies depending on the subject and experimental setup (Bahill et al., 1975b; Kapoula et al., 1986; Lehman and Stark, 1983). Comparisons of different eye tracking techniques showed that video-based eye trackers record the largest SDO signal (Choe et al., 2016; Kimmel et al., 2012; Mardanbegi et al., 2018; McCamy et al., 2015; Nystrom et al., 2013, 2016; Schmitt et al., 2007; Traisk et al., 2005). In the present study, we employed a video-based eye tracker, and the frequency of SDO is as follows: young subject: visually guided step saccade, 0.60; anti-saccades, 0.45; memory-guided saccades, 0.39; elderly healthy subject: visually guided step saccade, 0.72; anti-saccades, 0.63; memory-guided saccades, 0.58; PD: visually guided step saccade, 0.76; anti-saccades, 0.68; memory-saccades, 0.72; and MCI: visually guided step saccade, 0.75; anti-saccades, 0.68; memory-guided saccades, 0.74. In addition, the mean amplitudes of SDO in three tasks were less than 1°. Such results are comparable with previous reports (Bahill et al., 1975b) that also used video-based eye trackers.

Amplitude of the main saccades is not closely correlated with the occurrence of SDO

The relationship between the frequency/amplitude of the SDO and the amplitude of the main saccade is contradictory among previous studies. Although some studies have reported that the frequency of SDO is

negatively correlated with the amplitude of the main saccades (Bahill et al., 1975b; Kapoula et al., 1986; Van Gisbergen et al., 1981), controversial findings have also been reported (Fuchs, 1967; Kimmel et al., 2012). Similarly, the relationship between the SDO amplitude and the main saccade amplitude is also contradictory among previous studies. Some studies have reported that the amplitude of SDO is smaller when the amplitudes of the main saccades is larger (Hooge et al., 2015); however, others reported contradictory results (Bahill et al., 1975b; Kimmel et al., 2012). In the present study, the frequency and amplitude of SDO in the young subjects were greater in saccades with larger amplitudes ($>9^\circ$) than in saccades with smaller amplitudes ($<9^\circ$), whereas clear differences were not observed among the saccades with different amplitudes in the three groups of elderly subjects (Figure 3). Such results indicate that saccadic amplitude is not a sensitive parameter to assess the frequency of SDO, at least in the elderly subjects.

Peak velocity and deceleration of the main saccades are closely correlated with the occurrence of SDO

Reports have shown that, for similar amplitudes, main saccades with SDO have higher velocities and decelerations than those without SDO (Hooge et al., 2015; Kimmel et al., 2012; Mardanbegi et al., 2018). However, the correlation between SDO occurrence and saccadic peak velocity and deceleration regardless of amplitude has not been carefully studied. Examining this question would help clarify the importance of saccadic peak velocity and deceleration in assessing the frequency of SDO and, more importantly, in understanding the neural mechanisms of SDO generation. Our results show that saccades with SDO have higher peak velocity and deceleration than saccades without SDO (Figure 4) and the frequency and amplitude of SDO are positively correlated with the saccadic peak velocity and deceleration (Figure 5). We also classified two types of SDOs that showed varied spatiotemporal properties: SDO_{simple} and SDO_{complex}. Saccades with SDO_{complex} have higher peak velocity and deceleration than saccades with SDO_{simple}. Such results indicate that the peak velocity and deceleration of the main saccade are closely correlated with the occurrence of SDO.

Fraction of SDO_{complex} is dramatically lower in the young subjects than in the elderly subjects

The effect of aging on the frequency and amplitude of SDO was disputed among previous studies (Deubel and Bridgeman, 1995a; Mardanbegi et al., 2018). Our data show that, although the fraction of SDO was significantly lower in the young subjects than in the elderly subjects, a considerable number of SDOs were observed in the young subjects in all three tasks (Figure 2A). However, the fraction of SDO_{complex} in the young subjects was dramatically lower than that in the elderly subjects (Figure 2B). Such results indicate that, in comparing elderly subjects with young subjects, the most significant change in SDO is a greater fraction of SDO_{complex}.

To further seek the reason why elderly subjects show a higher frequency of SDO than young subjects, we analyzed the distribution of deceleration in four group subjects and in three tasks, respectively (Figure 6). We found that the elderly healthy, PD, and MCI groups show a higher proportion in SDO_{complex} and lower proportion in SDO_{without} than young subjects and are consistent in three tasks. It explained why elderly groups show higher frequency of SDO.

Similar frequency and amplitude of SDO among PD, MCI, and elderly healthy subjects suggest that the higher oculomotor structures do not directly develop SDO

An interesting finding in the present study is that the frequency and amplitude of SDO were not significantly different among the three groups of elderly subjects, i.e., there are no specific changes of SDO in PD and MCI compared with elderly healthy subjects (Figure 2). Because the primary pathological changes of PD and MCI occur in the basal ganglia and cerebral cortex, respectively, the higher oculomotor structures are commonly impaired in patients with PD and MCI (Briand et al., 1999; Ewencyk et al., 2017; Kahana Levy et al., 2018; Kato et al., 1995; Kaufman et al., 2010; Rivaud-Pechoux et al., 2007; Yang et al., 2013; Zola et al., 2013). Since there are no specific changes of SDO in patients with PD and MCI, it is more likely that SDO is generated by the lower oculomotor structures in the brainstem and cerebellum rather than the higher oculomotor structures. Thus, we propose that the higher oculomotor structures serve as a modulator rather than a generator in SDO generation, which affects SDO through modulating the activity of the lower oculomotor structures. A remaining question is why do patients with PD and MCI not show different modulating effects compared with elderly healthy subjects? One possible reason is that the modulating effect from the higher oculomotor structures to the lower oculomotor structures might be mild and limited; if the damage to the higher oculomotor structures is not severe enough, it will not

significantly affect the activity of the lower oculomotor structures and will not affect the occurrence of SDO. Further empirical experiments are required to test this possibility.

Lower frequency of SDO in voluntary saccades compared with reflexive saccades suggested the higher oculomotor structures modulating the SDO generation

To our knowledge, a direct comparison of the frequency of SDO between reflexive and voluntary saccades has not been performed. The present study shows that the frequency of SDO_{complex} is higher in reflexive saccades than in voluntary saccades (Figure 7A). Such results indicate that the higher oculomotor structures in the midbrain and cerebral cortex (which involved in voluntary saccade control) might affect the frequency of SDO by modulating the activity of lower oculomotor circuits in the brainstem and cerebellum, which reduces the saccadic velocity and deceleration (Figure 7B).

In the present study, a possible difference of neural control from higher to lower oculomotor structures between reflexive and voluntary saccades is as follows. In reflexive saccades, the onset of a visual target immediately induces a saccade toward it; thus, visual and saccadic activities overlap in time and location in higher oculomotor structures, such as the frontal eye field (Bruce and Goldberg, 1985), lateral intraparietal cortex (Zhang and Barash, 2000, 2004), and superior colliculus (Dorris et al., 1997). This more vigorous activity will evoke stronger discharge of oculomotor burst neurons in the brainstem and cause saccades with higher velocity and deceleration. In contrast, visual activity and saccadic activity are separated either in location (anti-saccades) or in time (memory-guided saccades); thus, the activity level in higher oculomotor structures is lower prior to the initiation of saccades compared with reflexive saccades. This less vigorous activity will evoke a lower discharge of oculomotor burst neurons in the brainstem and cause saccades with lower velocity and deceleration.

Potential neural mechanisms underlying SDO

Saccadic accuracy highly relies on the function of oculomotor structures in the brainstem and cerebellum (Optican and Pretegeiani, 2017; Van Gisbergen et al., 1981; Zee and Robinson, 1979). For instance, prior to each horizontal saccade, omnipause neurons in the pontine nucleus raphe interpositus release their inhibition to excitatory burst neurons in the paramedian pontine reticular formation, which monosynaptically project to motor neurons and internuclear neurons in the ipsilateral abducens nucleus. In turn, the abducens motor neurons project to the ipsilateral lateral rectus muscles, whereas the internuclear neurons project to the contralateral medial rectus motor neurons crossing the midline. In addition, the excitatory burst neurons drive ipsilateral inhibitory burst neurons that inhibit contralateral abducens excitatory burst neurons and motor neurons. Eventually, the innervation of motor neurons causes pulse-step changes in extraocular muscles, which drives eyes to change position (saccade) and hold still in a new position (fixation) (Shaikh et al., 2008). Thus, any improper interaction among the pre-oculomotor circuitry (omnipause burst motor neurons) will cause inaccurate saccades. Accordingly, research on the neural mechanisms underlying SDO have focused on investigating the interaction between burst neurons and omnipause neurons in the brainstem and the effect of cerebellar oculomotor neurons on burst and omnipause neurons (Bahill et al., 1975a, b; Ramat et al., 2005; Ramat et al., 2008; Shaikh et al., 2008). The basic idea of these models is that the imbalance of excitation-inhibition interaction between oculomotor burst neurons and omnipause neurons induces the post inhibitory rebound activity of burst neurons, which causes postsaccadic instability of the eyes, including SDO.

Limitation of the study

Since the present study is a psychophysical experiment, we did not directly assess the relationship between neural activity of oculomotor structures and the occurrence of SDO. Thus, the proposed mechanisms underlying SDO generation are based on our knowledge about the neural circuits of saccadic control.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.isci.2021.102764>.

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AUTHOR CONTRIBUTIONS

M.L., M.Z., and X.X. designed the experimental paradigms; M.L., J.W., W.M., and Z.Z. performed the experiments and analyzed the data; M.L. and M.Z. wrote the manuscript; and X.L., Z.L., and X.X. supervised the data collection and discussed the results.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Raw and analyzed data	This paper	https://doi.org/10.17632/wvrhfvchbp.1
Software and algorithms		
MATLAB	MathWorks, Natick, MA, USA https://www.mathworks.com/	RRID:SCR_001622
Psychtoolbox-3 (PTB-3)	Brainard DH. The Psychophysics Toolbox. <i>Spat Vis.</i> 1997;10(4):433-6. PMID: 9176952.	RRID:SCR_002881
SR Research EyeLink Eye Trackers	http://www.sr-research.com	RRID:SCR_009602

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Xin Xu, xuxinmm@hotmail.com.

Materials availability

This study did not generate any materials.

Data and code availability

- Original data have been deposited at Mendeley Data and are publicly available as of the date of publication. The DOI is listed in the [key resources table](#).
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Participants

The participants in this study included 23 young subjects, 38 elderly controls (no neurological disease), 38 PD patients and 35 MCI patients (The sample size was ascertained by using GPower software, effect size 0.4, α 0.05 and β 0.1, the power is 1- β , 0.9) (Faul et al., 2007). Informed consent was obtained from all subjects. The experimental protocol was approved by the Ethics Committee of Beijing Normal University and General Hospital of PLA (Medical School of Chinese PLA).

All participants completed the Folstein Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA). For PD subjects, the MMSE and MOCA tests were performed during medication administration (approximately 1 hour after taking levodopa and/or amantadine). In addition, the PD subjects were also tested with the Part 3 of Movement Disorders Society-revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) and the Hoehn and Yahr stage (H-Y stage) to assess their motor symptoms on and off medication (approximately 1 hour and 4 hours after taking medicine, respectively). The results for the PD subjects in the present study only show data in the 'off' medication state. The comparison between medication on and off states in PD will be the objective of another paper. MCI patients continued their regular medication routine. All the demographic data and clinical scores are shown in [Table S1](#). All participants had normal or corrected-to-normal vision.

METHOD DETAILS

Apparatus

Participants 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) with a

Table S1 Demographic and clinical data of each group

	Young	Elderly	PD	MCI
N (male/female)	23 (12/11)	38 (26/12)	38 (25/13)	35 (23/12)
Age (years)	22.38±3.49	70.90±9.89	62.37±7.54	74.91±9.0
MMSE	29.25±0.70	28.53±1.19	26.34±3.34	23.57±4.13
MOCA	28.00±1.22	24.23±3.30	21.62±5.30	19.95±3.17

Young, young healthy subjects; Elderly, elderly healthy subjects; PD, Parkinson's Disease subjects; MCI, Mild Cognitive Impairment subjects; MMSE, mini mental state examination; MOCA, Montreal Cognitive Assessment. Values presented are means \pm standard deviations.

1-kHz sampling rate. The visual stimuli were displayed on a 27-in. A BENQ monitor (XL2720-B; resolution: 1920×1084; refresh rate: 100 Hz) positioned 57 cm in front of the participants. The background luminance of the monitor is 0.08 cd/m², and the luminance of visual stimuli is 23.9 cd/m². 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). The recorded eye movement data were analyzed offline in MATLAB (R2018b; MathWorks, Natick, MA, USA).

Behavioral tasks

Visually-guided step saccade task (Figure S1A, left). Each trial began with a white cross (fixation point) appearing at the center of the screen for 800 ms. Simultaneously, with the disappearance of the fixation point, a white dot (target) appeared in one of four peripheral locations randomly (right, left, up and down; eccentricity of 10°). The size of the fixation point and target was 1° in length and diameter. Participants were instructed to fixate at the central cross (check window 4° in radius) and then make a saccade towards the target as accurately and rapidly as possible. The target disappeared after the eye entered and stayed in the check window (4° in radius) for 300 ms. A blank screen was interposed between trials with an interval of 800 ms.

Anti-saccade task (Figure S1A, middle). The anti-saccade task consisted of the same sequence of events as in the visually-guided step saccade task, except that the participants were instructed to make a saccade in the opposite direction (mirror location) of the target.

Memory-guided saccade task (Figure S1A, right). Each trial began with a white cross (fixation point) appearing at the center of the screen. Subjects needed to look at the fixation point immediately after its appearance and remained fixated as long as it was on. After 600 ms, a white dot randomly appeared at one of four peripheral locations (right, left, up and down; eccentricity of 10°) for 500 ms. Participants needed to keep the central fixation for an additional 600 ms (memory period) until it disappeared and then made a saccade to the location where the target appeared previously. A blank screen was interposed between trials with an interval of 800 ms.

These three tasks were run in separate blocks.

Classification of reflexive and voluntary saccades. In the visually-guided step saccade task (Figure S1B, left), a corrective saccade was the reflexive saccade.

In the anti-saccade task (Figure S1B, middle), participants made corrective saccades in some trials (voluntary saccades) but also frequently made errors, such as initiating a saccade towards the visual stimulus location first (reflexive saccades) and then a second saccade towards the task required location.

In the memory saccade task (Figure S1B, right), participants made corrective saccades towards the remembered target location after the go signal (voluntary saccades) in some trials but also frequently made saccades to the target immediately after its onset (reflexive saccades).

Classification of saccades with/without SDO. The method of identifying and classifying the SDO is as follows. The first step is to find all potential saccades along the horizontal and vertical directions of the eye trace in each trial. Potential saccades are detected based on the criteria of absolute velocity >15°/s and duration >10 ms. Then, saccades are combined together as one saccadic event if the intersaccadic interval

is <20 ms between adjacent saccades (Figures S2A and S1–S3). For each saccadic event, we take the end of the last saccade to the initiation of the following saccadic event or to the end of the eye trace if there was no saccadic event followed as the baseline and calculate the mean velocity as well as the standard deviation. The mean ± 2.58 times the standard deviation (99% confidence interval) are set as the dual thresholds (Figure S2B, e represents the dual thresholds). The dual thresholds serve as a criterion to assess whether a saccadic event contains SDO based on how many times its velocity surpasses the dual thresholds. Accordingly, the saccade events could be classified into 3 types. The first type is saccade without SDO (SDO_{without} , Figure S2B, left), i.e., its velocity only surpasses the dual thresholds once; the second type is saccade with simple SDO (SDO_{simple} , Figure S2B, middle), i.e., its velocity surpasses the dual thresholds two times; the third type is saccade with complex SDO (SDO_{complex} , Figure S2B, right), i.e., its velocity surpasses the dual thresholds three times.

Calculation of peak velocity and mean deceleration. Within each saccadic event (e.g., the SDO_{complex}), we defined the time at which the velocity surpasses dual thresholds as the saccade initiation or termination points (t1–6 in Figure S2B, right-down panel). Then, the median of t2 and t3 was the endpoint of the main saccade and the initiation of the first SDO. Similarly, the median of t4 and t5 was the endpoint of the first SDO and the initiation of the second SDO. The peak velocity of the main saccade was defined as the maximum absolute velocity between time t1 and the median point of t2 and t3. The mean deceleration of the main saccade was defined as the average deceleration between the time of peak velocity and the median of t2 and t3.

Calculation of the fractions of SDO and SDO_{complex} . The fraction of SDO was defined as the number of main saccades with SDO (both SDO_{simple} and SDO_{complex}) divided by the total number of correct response saccades in each task. We first calculate the fraction of SDO in each individual subject and then calculate the average SDO fractions in each group of subjects. The fraction of SDO_{complex} was defined as the number of main saccades with SDO_{complex} divided by the number of saccades with SDO.

QUANTIFICATION AND STATISTICAL ANALYSIS

p-values are included in results. Wilcoxon signed rank test was used to determine significance between two paired groups. Kruskal-Wallis test (one-way ANOVA on ranks) was used to determine significance between three groups or more. Statistical analyses were performed using MATLAB (R2018b; MathWorks, Natick, MA, USA).