



Altered transposition asymmetry in serial ordering in early Parkinson's disease[☆]

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ABSTRACT

Introduction: The ability to arrange thoughts and actions in an appropriate serial order is impaired in Parkinson's disease (PD). However, it is unclear how serial order is represented and manipulated and how the representation or manipulation is altered in the early stages of PD. We aimed to analyze the pattern of performance errors in serial ordering *versus* serial recall in nondemented PD patients with mild clinical symptoms and healthy adults to identify the underlying principles of serial ordering.

Methods: PD patients (N = 57) and healthy controls (N = 40) completed the adaptive digit ordering and digit span forward tests. We focused on items recalled in incorrect positions (transposition) and analyzed the tendency to recall transposed items too early (anticipation) *versus* too late (postponement). We also analyzed the tendency to recall the item displaced by the error (fill-in) *versus* the item following the error in the target output order (infill) after anticipation errors.

Results: PD patients not only made more transposition errors but also showed distinct error patterns. The patients made more anticipations but not postponements, and more fill-ins but not in fills than healthy controls in the ordering test (transposition asymmetry). Individual patients' percentage of anticipations was negatively correlated with their daily exposure to D2/3 receptor agonists. Patients' error pattern in the forward test was normal.

Conclusion: The increase in anticipations in PD suggests an increase in the forward-specific variability in the representation of serial order. Their increase in fill-ins suggests a deficit in the chaining mechanism involved in the manipulation of serial order.

1. Introduction

The ability to arrange thoughts and actions in an appropriate serial order is impaired even in the early stages of Parkinson's disease (PD). Medicated and drug-naïve PD patients with mild clinical symptoms often fail to understand the temporal relation of events expressed out of chronological order [1–3]. They are less efficient in planning sequential moves to solve complex problems [4,5]. Our previous work suggests

that the language and planning problems may result from a deficit in the manipulation of serial order in working memory [6]. In this study, we aimed to identify the underlying principles of serial ordering (*versus* serial recall) by analyzing the error pattern of patients' performance.

Earlier analyses of serial recall performance suggest that when confusing the position of an item, healthy adults tend to recall the item too early (anticipation, e.g., recalling item $i+1$ in position i , see Fig. 1) rather than too late (postponement, e.g., recalling item $i-1$ in position i).

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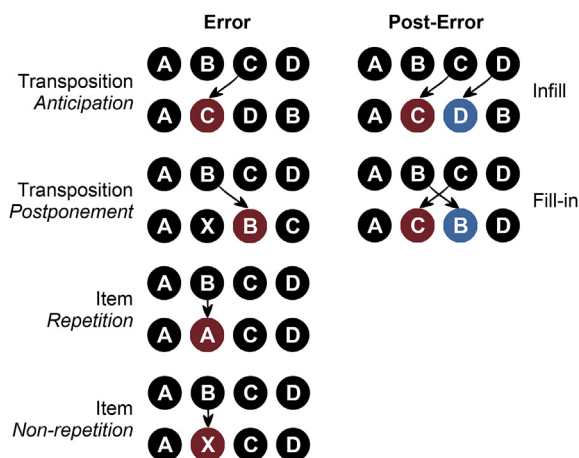


Fig. 1. Error types and examples. For each example, the upper row is the target output order and the lower row is the example error response.

The transposition asymmetry is independent of recall direction (e.g., forward or backward) and response modalities (e.g., spoken or typed) [7], but is consistent with the pattern of common speech errors [8]. Another feature of the asymmetry is that after the anticipation error, healthy adults tend to recall the item that was displaced by the error (fill-in, e.g., recalling item i after item $i+1$) rather than the item that follows the error in the target output order (infill, e.g., recalling item $i+2$ after item $i+1$). This feature is shared across species. The ratio of fill-in to infill errors in serial recall varies between 2:1 and 4:1 in humans [9,10] and rhesus macaques [11].

The transposition asymmetry is particularly informative for understanding how serial order is represented and manipulated in working memory. The preponderance of anticipation errors suggests that the stored items are more likely to drift forward than backward from their original position. The preponderance of fill-in errors can be accounted for by a primacy gradient mechanism complemented by response suppression [12]. It is proposed that the serial order is encoded in terms of a primacy gradient of activation levels. The activation of the first item is strongest and the activation of subsequent items decline monotonically towards the last item. The serial recall is accomplished via iterative processes. At each iteration, the most active item is selected for recall and then suppressed, so that the second strongest item becomes the most active item at the next iteration. If item $i+1$ is recalled too soon, item i will be a stronger competitor of item $i+2$ at the next recall position.

Different error patterns reflect different underlying principles. Here we analyzed the error pattern of non-demented patients with mild PD in the adaptive digit ordering task (DOT-A) versus digit span forward test to examine how the principles of serial ordering and serial recall are altered in early PD. First, we distinguished between transposition and item errors. A transposition error occurred when an item was recalled in an incorrect position, whereas an item error occurred when an item was incorrectly recalled. We expected an increase in transposition but not item errors in the DOT-A. Second, for transposition errors, we examined whether anticipation errors outweigh postponement errors in the DOT-A and how this asymmetry is changed in early PD. For anticipation errors, we examined whether fill-in errors outweigh infill errors in the DOT-A and how this asymmetry is changed in early PD. Third, we investigated the effect of dopamine D2/3 receptor agonists on performance errors. Previous studies showed a D2/3 receptor-mediated enhancement of serial ordering in healthy adults [13]. In particular, we expected a relation between individual patients' percentage of anticipation or fill-in errors and their daily exposure to D2/3 receptor agonists.

2. Methods

This study was approved by the ethical committee of Peking University Third Hospital in accordance with the Declaration of Helsinki. Each participant signed a written informed consent before participating in this study.

2.1. Patients and clinical assessment

We screened 132 patients with idiopathic PD (UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria) at the Peking University Third Hospital Department of Neurology. Inclusion criteria were 1) diagnosed with idiopathic PD for up to five years; 2) Hoehn-Yahr 1–3; 3) age 50–80 years; 4) education ≥ 9 years. Exclusion criteria were 1) a history of epilepsy, stroke or brain injury; 2) possible dementia (Montreal Cognitive Assessment, MoCA $< 21/30$) or taking acetylcholinesterase inhibitors (e.g., rivastigmine) or glutamatergic antagonists (e.g., memantine); 3) possible current depression (Beck Depression Inventory II, BDI-II > 7) or taking antidepressants (e.g., escitalopram). Fifty-seven PD patients were included in the analysis.

All patients were assessed on their regular antiparkinsonian drugs, including levodopa, pramipexole, piribedil, selegiline, amantadine, and entacapone. In addition to the levodopa actual dose and total levodopa equivalent dose, we calculated the levodopa equivalent dose for D2/3 receptor agonists to facilitate the analysis of drug effect [14].

The severity of motor symptoms was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) III (motor subscale). Note, we did not use the Movement Disorder Society revision of UPDRS because it had not been validated in mainland China when this study was approved. Global cognition was evaluated with the MoCA. Following the Level I assessment for diagnosing mild cognitive impairment (MCI) in PD [15,16], we distributed the patients into a PD group ($N = 30$, MoCA $\geq 26/30$) and a PD-MCI group ($N = 27$, $21 \leq \text{MoCA} \leq 25$). We conducted four neuropsychological tests in the working memory and language domains, including the adaptive digit ordering, digit span forward, digit span backward, and animal fluency tests. Other non-motor functions were assessed with the Non-Motor Symptoms Questionnaire, REM Sleep Behaviour Disorder Screening Questionnaire, Epworth Sleep Scale, and Insomnia Severity Index.

2.2. Healthy control subjects

We recruited 40 healthy elderly adults who had no history of significant neurologic or psychiatric disorders. They completed the same assessment for cognition and other non-motor functions as the patients.

2.3. Working memory tests and error types

All participants completed the auditory DOT-A [17] and digit span forward test. In the DOT-A, three to eight random digits were presented in each trial and participants were asked to recall the digits immediately in ascending order. This test resembled the digit span forward test in that: (a) it was adaptive regarding the length of each span and discontinuation after a failure within both trials of a particular span; (b) it was presented at a speed of one digit per second.

Participants' responses were defined relative to the target output order. We applied the strict scoring criteria [18] so that an item was counted correct only if recalled in its correct position and the analysis of error types was restricted to the initial error on each trial. Performance errors were binarily classified as transposition or item errors (Fig. 1). A transposition error occurred when an item was recalled in an incorrect position, whereas an item error occurred when an item was incorrectly recalled. Transposition errors were divided into anticipation and postponement errors. An anticipation error occurred when an item was recalled too early, whereas a postponement error occurred when an item was recalled too late. For anticipation errors, we analyzed the

post-error position, i.e. whether the error was followed by an item that preceded the error (fill-in) or an item that followed the error in the target output order (infill). Item errors were divided into repetition and non-repetition errors. A repetition error was the incorrect recall of an item already recalled in an earlier position. An increase in repetition errors reflects response suppression deficits.

Two researchers (S.M. and Z.Y.) coded error types independently. If an error fitted multiple types or the researchers did not agree on its type, the error was counted as ambiguous and excluded from further analyses. The proportion of ambiguous errors was less than 0.7% in either group and test.

2.4. Statistical analysis

Statistical inference was made using both null hypothesis significance testing and Bayesian model comparison with JASP. For each error type, the key parameter was the number of errors divided by the number of responses in the corresponding test. We first examined how transposition or item errors differed between groups using repeated measures ANOVAs. The ANOVA had a within-subject factor Test (DOT-A, forward), a between-subject factor Group (PD, PD-MCI, healthy control), and a covariate Age. The interaction between Test and Group was followed by two-sample *t*-tests (two-tailed, Bonferroni-corrected threshold $p < 0.025$).

For transposition errors, we then examined how anticipation or postponement errors, and fill-in or infill errors, differed between groups. For item errors, we examined how repetition errors differed between groups. The analyses were conducted using similar ANOVAs with Test and Group as factors and Age as a covariate.

We finally examined the effect of D2/3 receptor agonists by correlating the levodopa equivalent dose for D2/3 receptor agonists with the percentage of anticipation and fill-in errors in each test (Bonferroni-corrected threshold $p < 0.013$). The levodopa equivalent dose for other dopaminergic drugs and age were controlled.

3. Results

3.1. Test scores

Table 1 shows demographic and clinical features and neuropsychological measures of the patients and healthy controls. The one-way ANOVA revealed a group effect in the DOT-A and forward test. Consistent with our previous study [6], PD patients with normal global cognition scored lower than healthy controls in the DOT-A (pairwise comparison, $p < 0.001$) but not in the forward test. PD-MCI patients scored lower than healthy controls in both tests (DOT-A: $p < 0.001$; forward: $p = 0.001$).

3.2. Error types

Having confirmed our previous finding, we examined the group effect on each error type, using repeated measures ANOVAs with Test and Group as factors and Age as a covariate. Fig. 2A presents the percentage of transposition and item errors in each group. For transposition errors, the ANOVA revealed a significant interaction between Test and Group ($F(2,93) = 7.48$, $p = 0.001$, $\eta^2 = 0.14$) in addition to the main effect of Group ($F(2,93) = 4.61$, $p = 0.012$, $\eta^2 = 0.09$). Post-hoc *t*-tests showed that both PD and PD-MCI patients made more transposition errors than healthy controls in the DOT-A (PD: $t(68) = 2.44$, $p = 0.017$; PD-MCI: $t(65) = 5.47$, $p < 0.001$) but not in the forward test. There was no group effect for item errors or age effect ($ps > 0.22$). These results were confirmed by Bayesian model comparison (Table 2).

Fig. 2B presents the percentage of anticipation and postponement errors. Both patients and healthy controls tended to recall transposed items too early rather than too late. For anticipation errors, there was a significant interaction between Test and Group ($F(2,93) = 4.95$, $p = 0.009$, $\eta^2 = 0.10$) in addition to the main effect of Group ($F(2,93) = 5.17$, $p = 0.007$, $\eta^2 = 0.10$). Both PD and PD-MCI patients made more anticipation errors than healthy controls in the DOT-A (PD: $t(68) = 2.77$, $p = 0.007$; PD-MCI: $t(65) = 4.30$, $p < 0.001$) but not in the forward test. There was no group effect for postponement errors or age effect ($ps > 0.21$).

Fig. 2C presents the percentage of fill-in and infill errors. Both patients and healthy controls tended to recall the item that was displaced

Table 1

Demographic and clinical features, and neuropsychological measures (means, standard deviations, and group differences).

Features/Measures	PD (N = 30)	PD-MCI (N = 27)	Healthy controls (N = 40)	Group differences (<i>p</i> values)
Male: Female	16:14	16:11	20:20	0.76
Age (years)	67.6 (7.0)	71.9 (8.0)	66.5 (5.8)	0.12
Education (years)	14.6 (2.7)	14.2 (3.8)	14.4 (2.0)	0.54
<i>Motor symptoms</i>				
Duration of disease (years)	1.9 (1.8)	2.3 (1.8)	–	0.98
Hoehn and Yahr Scale	2.0 (0.6)	2.1 (0.5)	–	0.49
UPDRS III: Motor	12.1 (4.6)	10.8 (3.0)	–	0.41
<i>Cognition</i>				
MoCA	27.4 (1.2)	24.1 (1.0)	28.2 (1.4)	< 0.001*
Adaptive digit ordering	5.4 (2.2)	3.8 (1.7)	7.4 (2.2)	< 0.001*
Digit span forward	7.5 (1.2)	7.0 (1.2)	8.1 (1.0)	0.001*
Digit span backward	4.5 (1.1)	4.1 (1.0)	5.8 (1.8)	0.001*
Animal fluency	19.3 (5.1)	15.1 (3.2)	21.2 (5.8)	0.003
<i>Other non-motor functions</i>				
Non-Motor Symptoms Questionnaire	9.5 (4.6)	10.8 (4.7)	–	0.57
Beck Depression Inventory II	2.2 (2.2)	3.4 (2.0)	1.9 (1.9)	0.16
REM Sleep Behaviour Disorder Screening Questionnaire	4.7 (2.6)	5.4 (3.5)	1.9 (1.4)	0.001*
Epworth Sleep Scale	5.6 (4.5)	3.7 (3.7)	3.8 (2.6)	0.13
Insomnia Severity Index	4.1 (3.9)	4.3 (6.5)	3.0 (2.6)	0.64
<i>Levodopa equivalent daily dose (LEDD)</i>				
Total (mg)	272.1 (159.9)	312.2 (181.5)	–	0.62
Levodopa (mg)	146.7 (146.2)	223.2 (152.9)	–	0.16
D2/3 receptor agonists (mg)	50.4 (45.1)	44.9 (44.9)	–	0.11

MCI, mild cognitive impairment; group differences, *p* values of one-way ANOVAs or Kruskal-Wallis one-way ANOVAs as appropriate; asterisks (*), significant differences thresholded at $p < 0.0025$ (Bonferroni correction); UPDRS, Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment.

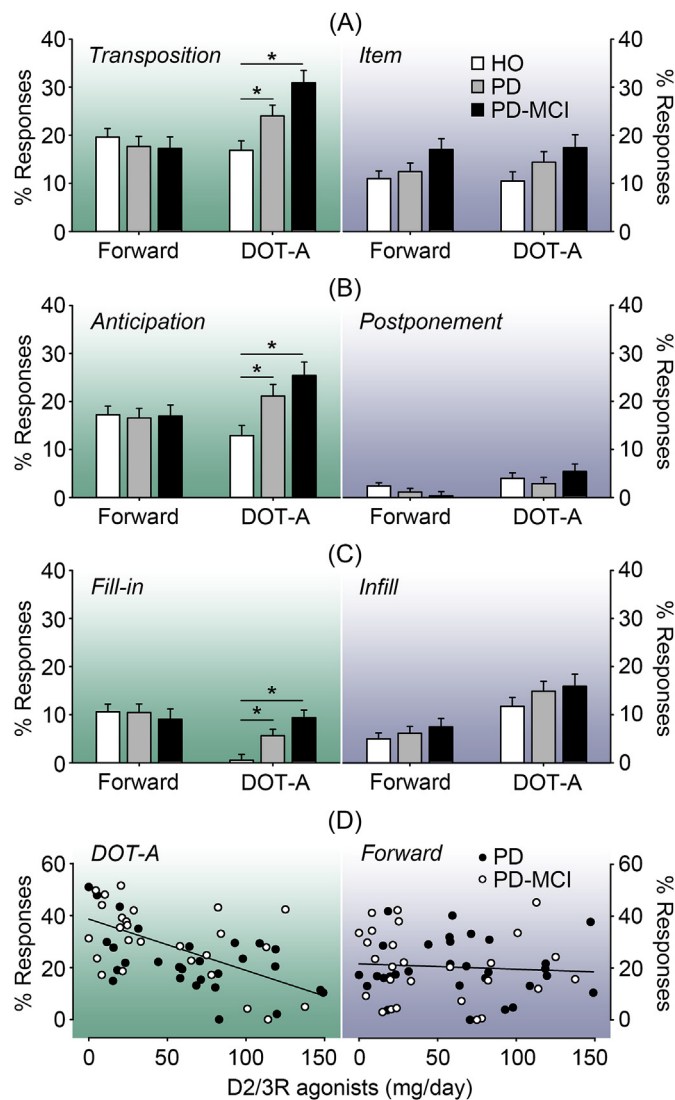


Fig. 2. Mean percentages and standard errors of (A) transposition and item errors, (B) anticipation and postponement errors, and (C) fill-in and infill errors for the adaptive digit ordering test (DOT-A) and digit span forward test in PD patients with normal global cognition (PD) or with mild cognitive impairment (PD-MCI) and in healthy controls (HC). The mean values were age-adjusted. Asterisks (*) indicate significant differences between patients and controls ($p < 0.05$). (D) The percentage of anticipation errors was negatively correlated with the levodopa equivalent dose for D2/3 receptor agonists in the DOT-A but not in the forward test.

by the error in the forward test. The fill-in:infill ratio was approximately 2:1. In contrast, they tended to recall an item that followed the error in the target output order in the DOT-A. For fill-in errors, there was a significant interaction between Test and Group ($F(2,93) = 4.70$, $p = 0.011$, $\eta^2 = 0.09$). Both PD and PD-MCI patients made more fill-in errors than healthy controls in the DOT-A (PD: $t(68) = 3.06$, $p = 0.005$, PD-MCI: $t(65) = 4.54$, $p < 0.001$) but not in the forward test. There was no group effect for infill errors or age effect ($ps > 0.21$).

Within item errors, repetition errors were rare in either group and did not differ significantly between groups (HC: 2.2%; PD: 2.0%; PD-MCI: 3.2%).

3.3. Effect of D2/3 receptor agonists

Fig. 2D illustrates the effect of D2/3 receptor agonists on anticipation errors. The levodopa equivalent dose for D2/3 receptor agonists was negatively correlated with the percentage of anticipation errors in the DOT-A ($r = -0.56$, $p < 0.001$) but not in the forward test ($p = 0.59$). The patients who took a greater dose of D2/3 receptor agonists tended to make fewer anticipation errors during serial ordering. However, no correlation was obtained for fill-in errors ($ps > 0.10$).

4. Discussion

In this study, we analyzed the performance of serial ordering and serial forward recall in non-demented patients with mild PD and healthy adults. The error pattern analysis enables the inference of underlying principles which cannot be inferred from test scores. PD patients with normal global cognition made more transposition errors than healthy adults in the DOT-A, confirming that the ability to rearrange working memory representations is impaired in early PD. Both PD patients and healthy adults tended to recall transposed errors ahead of their correct positions in the DOT-A and forward test. This tendency was enhanced in PD patients, leading to a disproportionate increase in anticipation errors during serial ordering. Moreover, PD patients' anticipation errors were negatively correlated with their daily exposure to D2/3 receptor agonists. After anticipation errors, both PD patients and healthy adults tended to recall the item that was replaced by the error in the forward test, which is consistent with earlier studies of serial recall performance in primates. In the DOT-A, in contrast, PD patients and healthy adults tended to recall the item that followed the error in the target output order, suggesting that distinct principles are involved for serial ordering *versus* serial forward recall. More importantly, this tendency was reduced in PD due to a disproportionate increase in fill-in errors during serial ordering.

Most existing computational models for serial recall emphasize the encoding and retrieval of original sequences [12,19–21] and do not adequately account for the flexible manipulation of serial order. The altered transposition asymmetry is informative not only for identifying the preferred principles of serial ordering but also for understanding the

Table 2
Bayesian model comparison.

Models	Bayes factors (BF ₁₀)					
	Transposition	Item	Anticipation	Postponement	Fill-in	Infill
Test	3.34	193.54	0.25	45.69	9.95×10^3	6.10×10^5
Group	1.77	0.21	3.58	0.13	0.65	0.23
Test + Group	6.22	43.91	0.92	6.01	8.11×10^3	1.78×10^5
Test + Group + Test × Group	1.97×10^3	22.90	27.33	1.50	1.37×10^5	2.44×10^4
Age	0.29	0.39	0.41	0.22	0.25	0.25
Test + Age	1.00	79.91	0.11	10.53	2.68×10^3	1.65×10^5
Group + Age	0.38	0.06	0.90	0.03	0.13	0.05
Test + Group + Age	1.34	13.73	0.24	1.57	1.71×10^3	3.72×10^4
Test + Group + Age + Test × Group	399.36	7.62	6.88	0.41	2.87×10^4	4.96×10^3

initial changes of serial ordering in early PD. Our finding that anticipation errors outweighed postponement errors in both tests suggests that the stored items are more likely to drift forward than backward regardless of behavioral goals. PD's increase in anticipation errors during serial ordering suggests that the variability in remembering positions increases and therefore, the precision of working memory representations for ordinal positions decreases in early PD.

Our finding that fill-in errors outweighed infill errors by a ratio of 2:1 in the forward test in the patients supported the hypothesis that serial recall is intact in early PD. However, this transposition asymmetry was reversed in the DOT-A in both PD patients and healthy adults, which has not been reported in previous studies. The reversed asymmetry is against the principle of a primacy gradient which predicts more fill-in than infill errors. Instead, a chaining mechanism is necessary to accommodate the preponderance of infill errors during serial ordering. One possibility is that serial ordering is realized in two stages [22]. At the first stage, all items are simultaneously activated and contiguous associations are formed between the items based on ordinal knowledge or a newly learned arbitrary rule. At the second stage, the mechanism retrieves sequential items, using the associations between items as the retrieval cues. In this case, an anticipation error will subsequently cue the item that follows the error in the target output order more strongly than any other items. The chaining mechanism may be employed specifically for serial ordering while the gradient mechanism may be the default. In early PD, the chaining mechanism may be partially impaired and the gradient mechanism biases the system towards fill-in errors. It is worth noting that fill-in errors increased but not outweighed infill errors during serial ordering in the patients, suggesting that the chaining mechanism has not been totally impaired in early PD.

Neurochemical mechanisms of serial ordering are still unclear. Dopamine plays an important role in visuospatial working memory, with D1 receptors involved in the maintenance of representations and D2 receptors in the flexible updating of task-relevant information [23,24]. However, evidence for a similar modulatory role of dopamine in temporal working memory is insufficient and conflicting. For example, Cooper et al. improved serial ordering performance by stimulating D2 receptors [25], whereas Dodds et al. boosted the performance by blocking D2 receptors [13]. A novel finding of this study is the beneficial effect of D2/3 receptor agonists on anticipation errors. PD patients who took a greater levodopa equivalent dose of pramipexole and/or piribedil tended to make fewer anticipation errors during serial ordering. We hypothesize that stimulating D2/3 receptors may reduce the forward drifting probability and increase the fidelity of working memory representations for ordinal positions. This hypothesis is consistent with a study by Fallon et al. [26] which showed that the D2 receptor agonist can reduce the variability in remembering orientations and increase the precision of recalled orientations, but needs to be tested in future pharmacological intervention research.

Last but not least, we observed that repetition errors were equally rare in PD patients and healthy adults. This finding suggests that the suppression of recalled items was preserved in early PD. PD's deficit in serial ordering cannot be attributed to response disinhibition.

This study has limitations. We focused on serial ordering in working memory in PD, but the serial ordering problem also exists in other cognitive domains [27,28] and in other neurological diseases [29,30]. However, few patient studies included a systematic analysis of serial ordering errors. It is unclear whether the altered transposition asymmetry we observed can be generalized to sequence learning, or whether it is specific for PD. We believe a wider application of error pattern analysis will reveal the unique and common mechanisms underlying the serial ordering problem across cognitive domains and neurological disorders.

5. Conclusion

Serial ordering is impaired in early PD. PD patients not only made more transposition errors than healthy adults but also showed distinct error patterns. PD patients were more likely to recall transposed items too early (anticipation errors), suggesting an increase in the variability in remembering ordinal positions (i.e. larger forward drifting probability) and a reduction in the precision of working memory representations for serial order. Dopamine D2/3 receptor agonists may reduce anticipation errors via modulating the forward drifting probability. After anticipation errors, PD patients showed an enhanced tendency to recall the item that was displaced by the error (fill-in errors), suggesting a deficit in the chaining mechanism involved in serial ordering.

6. Authors' roles

Shaoyang Ma acquired and analyzed the data, and revised the article.

Yingshuang Zhang acquired the data and revised the article.

Na Liu acquired the data and revised the article.

Weizhong Xiao acquired the data and revised the article.

Shuaqi Li acquired the data and revised the article.

Guanyu Zhang acquired and analyzed the data, and revised the article.

Xiaolin Zhou acquired the data and revised the article.

Thomas F. Münte conceptualized and designed the study, and revised the article.

Zheng Ye conceptualized and designed the study, acquired and analyzed the data, and drafted the article.

All authors approved the final version.

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The authors declared no conflict of interest.

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