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博　士　論　文

The effects of visual, auditory, and mixed cues
on choice reaction in Parkinson's disease
（視覚，聴覚，混合感覚刺激がパーキンソン病患者の
選択反応に及ぼす影響に関する研究）

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論文内容の要旨

領　　域　リハビリテーション科学

分　　野　脳機能・精神障害学

氏　　名　赤松智子

論文題目

The effects of visual, auditory, and mixed cues on choice reaction in Parkinson's disease
（視覚，聴覚，混合感覚刺激がパーキンソン病患者の選択反応に及ぼす影響に関する研究）

論文内容の要旨

本論文では，視覚，聴覚，混合感覚刺激がパーキンソン病（Parkinson's disease ; 以下 PD）患者の選択反応に及ぼす影響について調べた。

対象は，PD と診断され抗 PD 薬を 1 年以上服用している PD 患者 30 名（男性 14 名，女性 16 名，40～74 歳 ; 平均年齢 60.4±9.8 歳）で，平均教育年数は 13.5±3.2 年であった。臨床症状は，Hohen and Yahr の分類では StageⅢ（平均 2.3±0.5）以下であり，発症後の経過年数は 9.2±6.6 年である。PD 患者は，抗 PD 薬を服用し薬効ピーク時に検査を試行した。Unified Parkinson Disease Rating Scale(UPDRS) on 時の平均スコアーは 29.2±12.2，off 時の平均スコアーは 36.8±12.9 であった。健常対照者（以下 HC）は，20 名（男性 6 名，女性 14 名，40～68 歳 ; 平均年齢 58.6±7.2 歳）で，平均教育年数は 12.7±2.3 年であった。明らかな認知機能障害や過去に脳血管性障害など中枢神経疾患既往のある者は除外した。全員右利きであり，年齢及び性別，教育年数，MMSE，WAIS-R，WF において PD 群と HC 群間に有意な差はみられなかった。

方法は，携帯型パーソナルコンピューターを用いて後出しじゃんけん課題を行った。提示方法には，視覚刺激，聴覚刺激，聴覚の妨害刺激が混入している視覚刺激，視覚の妨害刺激が混入している聴覚刺激の４種の感覚刺激で課題を提示するように準備した。被験者には，提示された刺激課題に対して「勝ち」，「あいこ」もしくは「負け」となるよう可能な限り早く反応するよう指示した。結果の解析には，刺激提示から回答までの反応時間とその結果について測定し，反応時間と誤数率について比較した。さらに PD 群の動作緩慢や無動といった運動機能の影響を考慮し，「勝ち」と「負け」の結果から，それぞれ「あいこ」に要した時間を差し引いた修正反応時間を算出し両群を比較した。

結果は，PD 群，HC 群ともに「あいこ」，「勝ち」，「負け」の順に反応時間の延長と誤数率が増加する傾向が認められた。PD 患者の運動機能の影響を考慮した修正反応時間の比較では，聴覚刺激時の「負け」において HC 群より延長し，視覚の妨害刺激が混入する聴覚刺激時において大幅な延長が見られた。

以上の結果から，PD 患者は特に聴覚よりも視覚による刺激に対して HC 群よりも影響を受けやすく，なかでも習慣的な行動を覆すよう要求される刺激反応不適合性を伴う状況下では，より影響を受ける傾向にあることが示唆された。PD 患者に対する効果的なリハビリテーションプログラム作成には，長期学習され文脈上も適合性のある反応を視覚刺激によって抑制しないよう内容を考慮することが重要と考えられる。

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The effects of visual, auditory, and mixed cues on choice reaction in Parkinson's disease

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Abstract

We investigated the effects of visual, auditory, and mixed cues on complex choice reaction in people with Parkinson's disease (PD). The paradigm using a computerized task was based on a game, "paper-rock-scissors." Four types of sensory cues were employed: simple visual cues, auditory cues, visual cues with auditory distracters, and auditory cues with visual distracters. Subjects were instructed to win, draw, or even lose the games and were required to respond as soon as possible after the sensory cues. When bradykinesia was taken into account, the PD patients had slower motor reactions. Further, when asked to lose in response to auditory cues, they displayed a significant delay in cognitive processing as compared to the healthy controls (HC), with a greater delay in the presence of a visual distracter. The error rates in the PD group were significantly higher than those in the HC group. These results suggest that PD patients are more influenced in choice reaction than the HC and by visual rather than auditory cues, especially under conditions with stimulus-response incompatibility that requires overriding habitual behavior. These data may be helpful in designing effective rehabilitation programs for PD to avoid inhibition of overlearned and contextually compatible reactions with visual distracters.

Key words: Parkinson's disease; cognition; executive function; choice reaction; cue; stimulus-response compatibility

1. Introduction

It is well-known that Parkinson's disease (PD) is caused by a nigrostriatal dopamine deficiency that results in the dysfunction of the basal ganglia-frontal lobe circuitry [1,2]. The classic PD symptom triad of resting tremor, rigidity, and bradykinesia attests to the centrality of the motor symptoms of the disease. Recently, mild cognitive or psychiatric impairments such as bradyphrenia and depression have gained recognition as important issues in the treatment of PD patients recovering from a lengthy illness, in order to improve their quality of life (QOL [3,4]). Cognitive or behavioral impairments in PD indicate that these deficits may be related in some way to the circuit [5,6] between the frontal lobe and basal ganglia, both of which are involved in the selection and inhibition of competing responses [7]. Such reduced inhibition and behavioral impairments have been identified in neuropsychological executive tasks such as Word Fluency (WF), the Trail Making Test (TMT), the Wisconsin Card Sorting Test (WCST [8-10]), and complex tasks containing interfering stimuli [11,12]. The executive dysfunction in PD has not been regarded as important in daily life activities that require cognitive judgments or decisions; the dysfunction, however, has now been shown as one of the important factors in maintaining good QOL [13,14]. Further, these cognitive or psychiatric dysfunctions barely respond to medical treatments with L-dopa or dopamine agonists [15,16].

Such cognitive executive impairments become more obvious when PD patients attempt to begin movements. That movements of PD patients are less disturbed when triggered by visual or auditory stimuli is a well-known phenomenon known as paradoxical kinesis. Although rehabilitation clinicians have utilized this phenomenon to facilitate functional activities such as gait in PD patients, clinical research on the effectiveness of visual or auditory cues on PD mobility is limited [17–22]. However, the effect of such sensory cues on the cognitive functions of PD patients has been the focus of several reports [23–28].

The purpose of the present study was to examine the speed or accuracy of choice reaction with or without sensory distracters in patients with PD. A complex game that required the comprehension of rules (win, draw, or loss in the game of paper-rock-scissors) was played using visual or auditory cues. In addition, the rules were slightly modified, such that subjects were required to lose the game intentionally as well as to win or to draw, and visual or auditory cues were paired with auditory or visual distracters, respectively.

2. Subjects and methods

2.1. Subjects

The participants of this study constituted 30 idiopathic PD patients (14 males and 16 females) with an average age of 60.4 ± 9.8 years (mean ± standard deviation, range: 40–74 years) and 20 healthy age-matched controls (HC; 6 males and 14 females) with an average age of 58.6 ± 7.2 years (range: 40–68 years). Neurologists specializing in movement disorders established the diagnosis of idiopathic PD. None of the HC subjects presented a history of major medical, neurological, or psychiatric disorders or a family history of PD. The two groups did not differ statistically in terms of age, gender, educational history, and handedness (Table 1). The PD patients were recruited from PD support groups in local communities, and the HC were either friends or partners of the PD patients. All of the subjects were informed about the details of the study, and they agreed to participate with written informed consent. All the procedures in this study were performed strictly according to the local Ethics Committee's Clinical Study Guidelines and were approved by the internal review board.

The clinical characteristics and medication of the PD patients are shown in Table 2. The duration of the disease in the patients was 3–35 (9.2 ± 6.6) years. The clinical evaluation of motor symptoms for the PD group fell within the mild to moderate range, as defined by the Hoehn and Yahr symptom severity rating scale—between 1 and 3 degrees (2.3 ± 0.5)—and by the complete Unified Parkinson Disease Rating Scale (UPDRS; 29.2 ± 12.2 in the on state and 36.8 ± 12.9 in the off state). One patient was taking only L-dopa (daily dose: 600 mg), while the other 29 subjects were taking a dopa decarboxylase inhibitor in combination with L-dopa (mean daily dose: 357.8 ± 123.8 mg), together with various doses of dopamine agonists. Medications such as benzodiazepine, antidepressants and anti-cholinergic drugs, which might affect attention, were not used in these patients. All the tests were performed when the patients were taking their regular medication and during the peak effect of the medication (on condition).

2.2. Neuropsychological evaluation

Neuropsychological and psychometric examinations were performed on all subjects. The Japanese versions of the Mini-mental State Examination (MMSE) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) were used to evaluate the general intellectual functions of the subjects. The WF test, which consisted of two subsets, assessed the verbal executive function. In the semantic condition (SWF), the subjects were required to produce as many names of animals as possible within 1 min. In the phonemic condition (PWF), nouns beginning with the letter "ka" were required. The TMT, which consisted of both the "A" and the "B" form, was performed to evaluate executive function. TMT-A is a test in which numerals from 1 to 25 are written within scattered circles. The subjects are instructed to draw lines connecting the numerals in order as quickly as possible. TMT-B is a more complex test using the numerals from 1 to 13 and the Japanese kana characters for "a", "i", "u", "e", "o", "ka", "ki", "ku", "ke", "ko", "sa" and "shi", which correspond to first 12 kana characters listed in the Japanese 50-character syllabary written within circles. The subjects are instructed to draw lines connecting the numerals and kana characters in order, alternating numeral and kana (e.g., "1"-"a"-"2"-"i"-"3", etc.). While TMT-A assesses speed of performance, visual search, and mental tracking, TMT-B estimates not only the same cognitive processes as TMT-A, but in addition demands multitasking, simultaneous processing, and cognitive flexibility. The fifteen-item Geriatric Depression Scale (GDS15) was used to evaluate the depressive states of the subjects.

2.3. Choice reaction task

The paradigm was based on "paper-rock-scissors" or "paper-stone-scissors," which is traditionally played as "Janken" in Japan. The Japanese people are quite familiar with this game, which might be played as frequently as the toss of a coin in the West. The rules are as follows: paper beats rock, rock beats scissors, and scissors beat paper. The same responses among players indicate a draw.

The experimental paradigm is illustrated in Fig. 1. We used two types of sensory cues to investigate the effect of a simple visual or auditory cue and of one target cue combined with another distracting cue on the choice reaction task. The four types of sensory stimuli were as follows: (1) a single simple visual cue of a picture of a hand that imaged paper, rock, or scissors (V); (2) a single simple auditory cue of a human voice that announced "paper," "rock," or "scissors" (A); (3) a mixed stimuli of a visual cue presented simultaneously with an auditory cue as a distracter (V+); and (4) a mixed stimuli of an auditory cue with a visual distracter (A+). In the case of the visual cue with an auditory cue as a distracter (V+), the different or same voice (paper, rock, or scissors) was simultaneously provided to the subject along with the presentation stimulus (paper, rock, or scissors). The subjects were requested to push the button and follow the rules (win, loss, or draw) with the presentation stimulus. The visual cues were presented in the center of the display of a laptop personal computer (PC; Sharp, Osaka, Japan), so that the subjects could easily recognize each stimulus at the center of the visual field without moving their eyes and possible ocular movement disturbance could be negligible in PD patients. The angles of the stimuli in the center of the visual field were within 14 degrees in the vertical and 16 degrees in the horizontal direction. As for the auditory cues, the subjects heard one of the three words in Japanese, which indicated the shape denoted by the hand through the PC speakers. In the case of the mixed stimuli, the visual cue (for instance, scissors) was presented simultaneously with an auditory distracter (paper or rock) or the same word (scissors).

The subjects were requested to respond to the sensory cues as quickly as possible by using the input switch (Jonan Electric, Kyoto, Japan) with their right hand, which was the dominant side in all subjects, as confirmed by using the Edinburgh Handedness Inventory. The input switch of box type had three buttons at intervals of 25 mm, each of which was labeled "paper," "rock," and "scissors." All the subjects were pre-trained in using the PC until each subject fully understood the choice reaction task. The reaction time was measured from the point the cue was provided to the time when the subject pushed a button. The subjects were never explicitly informed whether their responses were correct or otherwise. The reaction times and contents of both the stimuli and the responses were recorded and analyzed by using the PC.

Each subject performed 216 trials of the paper-rock-scissors task; these trials were divided into four blocks of 54 trials wherein the subject played in response to one of the four types of sensory cues. Each block was further divided into three sessions wherein the subject was variously instructed to comply with the rules. Each session consisted of three parts of six trials under randomly assigned conditions.

2.4. Statistical analyses

The results of the neuropsychological evaluations were compared between the PD and HC groups using Mann-Whitney's U-test. The mean reaction time (seconds) and error rate (%) of each subject were calculated from the results of the choice reaction task, which were recorded on the PC. Subsequently, in order to reduce the effect of motor dysfunction in PD, when comparing the reaction times between the HC and PD groups, we subtracted the reaction times in the draw condition from those in the win or loss conditions. We referred to these differential times thus: W-D time for win and L-D time for loss.

To assess the effect of three types of outcome rules (win, loss, or draw) within each cue, a repeated-measures Group (2) x Rule (3) 2-way analysis of variance (ANOVA) for each cue condition was conducted for the reaction time and error rate. A similar ANOVA (2 groups x 2 rules) was conducted within each cue condition for the calculated reaction time, W-D, or L-D time. Finally, to assess the effect of the four types of sensory cues (V, A, V+, and A+) within each rule, a Group (2) x Cue (4) ANOVA was conducted for the reaction time and error rate. When the results of ANOVA were significant, post hoc multiple comparisons were conducted using Wilcoxon's signed rank test or a t-test with Bonferroni corrections. All statistical analyses were performed using the Statistical Program for the Social Sciences (SPSS, Chicago, IL). Differences with a value of $p < 0.05$ were considered as being statistically significant.

3. Results

3.1. Neuropsychological disorders

The results obtained from the neuropsychological examinations on subjects for the screening of cognitive or psychological disorders are shown in Table 1. The PD and HC groups were matched well for MMSE, WAIS-R, and WF. Eventually, there was no difference in the time required by both groups to learn the rules. The mean scores were significantly lower on the TMT-A ($p = 0.002$) and the TMT-B ($p=0.02$) tests, and significantly higher for GDS15 ($p = 0.001$) in PD patients than in the controls.

3.2. Reaction delays

The differences in the reaction time between two groups were analyzed for each of the rules and sensory cues. A Group x Rule 2-way ANOVA revealed a significant interaction effect only for simple auditory cues ($F = 8.612$; $df = 2, 96$; $p < 0.001$) as well as highly significant main effects of rule (within subjects: $F (2, 96) = 307.5$, 190.7, 93.4, and 280.5 for V, A, V+, and A+ cues, respectively; $p < 0.001$) and group (between subjects: $F (1, 48) = 5.698$, $p = 0.021$ for V; $F (1, 48) = 14.49$, $p < 0.001$ for A; $F (1, 48) = 8.373$, $p = 0.006$ for V+; and $F (1, 48) = 4.51$, $p = 0.039$ for A+ cues) for all cues. A post hoc test revealed that in all the rules, PD patients (closed circles with thick solid lines) exhibited a significantly longer reaction time than did the controls (open circles with thin dotted lines). Further, in both groups, the reaction time was the longest for loss and longer for a win than for draw, as seen in Fig. 2.

Fig. 3. displays the calculated reaction times of W-D or L-D in response to the sensory cues, representing the presumed time lags in mental processing for win or loss in the HC and

PD groups. PD patients required a longer calculated reaction time than controls, and L-D time was longer than W-D time within each sensory cue. A 2-way ANOVA revealed a significant interaction effect only for simple auditory cues ($F(1, 48) = 7.573$; $p = 0.008$) as well as highly significant main effects of rule for all cues (within subjects: $F(1, 48) = 170.6$, 47.28, 23.79, and 86.53 for V, A, V+, and A+ cues, respectively; $p < 0.001$) and group only for simple auditory cues (between subjects: $F(1, 48) = 9.834$; $p = 0.003$). Post hoc analyses revealed that in the case of responding to the auditory cue, L-D time was significantly longer in the PD group than in the HC group ($p < 0.01$), while no apparent differences were observed between the two groups in the case of responding to the other sensory stimuli. The calculated reaction time was the longest when the subjects were requested to lose in response to auditory cues.

The effect of the four types of sensory cues was also assessed, and a Group x Cue 2-way ANOVA revealed a significant interaction effect only for loss ($F(3, 144) = 4.826$; $p = 0.003$) as well as highly significant main effects of cue (within subjects: $F(3, 144) = 21.76$, 9.588, and 34.8 for loss, draw, and win, respectively; $p < 0.001$) and group (between subjects: $F(1, 48) = 8.607$, $p = 0.005$ for loss; $F(1, 48) = 9.412$, $p = 0.004$ for draw; and $F(1, 48) = 8.062$, $p = 0.007$ for win) for all cues. These effects were observed not only on the simple reaction time but also on the calculated reaction time (Table 3A). A Group x Cue 2-way ANOVA showed a significant interaction effect only for the loss rule ($F(3, 144) = 7.102$; $p < 0.001$) as well as highly significant main effects of cue for both loss and win rules (within subjects: $F(3, 144) = 24.18$ and 25.74 for loss and win, respectively; $p < 0.001$). In the case of responding to the auditory cues without visual distracters, L-D time in the PD group was significantly longer than that in the HC group, as seen in Fig. 3.

3.3. Reaction error rates

An assessment of the error rates in these tasks was performed for each of the outcome rules and sensory cues in both the HC and PD groups. PD patients generally exhibited higher error rates than did the controls, as seen in Fig. 4. A Group x Rule 2-way ANOVA on the error rates showed a significant effect of rule ($F = 2.929$, $p = 0.036$ for win), and post hoc tests demonstrated that when the subjects were asked to lose, the error rates were significantly higher in the PD group than in the HC group ($p < 0.01$ or $p < 0.05$). Significant differences in the error rate were also observed among the rules in both groups, and within each cue, the error rate was highest for loss and higher for win than it was for draw ($p < 0.01$ or $p < 0.05$).

A Group x Cue 2-way ANOVA revealed significant main effects of sensory cue on the error rates for loss ($F = 3.675$, $p = 0.029$ for visual cues; $F = 3.481$, $p = 0.035$ for auditory cues). A post hoc analysis revealed that in both the groups, the error rate for responding to the auditory cues with visual distracters was significantly higher than that for responding to the visual cues with auditory distracters when asked to lose ($p < 0.05$).

When the visual cues were presented with the auditory distracters, the increase in error rate was not significant since the error rate was high even when asked to draw. The highest error rates were observed in the PD group when responding to the auditory cues with visual distracters and when instructed to lose.

3.4. The effect of distracters

With regard to the effect of sensory distracters on the calculated reaction time, significant differences between the reactions with and without distracters were observed in both groups when asked to lose ($p < 0.01$ or $p < 0.05$, Table 3A), while no significant effects of the distracters were observed when instructed to win. In the HC group, L-D time was significantly longer when responding to auditory cues with visual distracters than when responding to cues without the distracters ($p < 0.05$), but not in the case of responding to visual cues with auditory distracters. Under these conditions, the sensory distracters shortened the calculated reaction time ($p < 0.01$).

The sensory distracters significantly affected the number of reaction errors under many conditions (Table 3B). When asked to draw or lose in response to an auditory cue, the addition of a visual distracter caused significantly more errors in both the HC group ($p < 0.05$; Table 3B) and the PD group ($p < 0.01$). In the PD group, the error rates were also significantly increased by the distracter when asked to win with both visual ($p < 0.01$) and auditory cues ($p < 0.05$).

4. Discussion

Executive dysfunctions and other cognitive impairments have been recognized as acting synergistically with motor impairments to lower the QOL of PD patients [3,4,13,14]. The purpose of this study was to investigate whether the processing of sensory information for complex choice reaction was altered in PD patients, since such alteration might be associated with functional impairments in their daily lives [29]. We employed the gambling-type paper-rock-scissors game as the choice reaction task since we noted that in their recreational activities, PD patients appeared to have a predilection for the game. Under all conditions, the motor reactions of the PD group to the sensory cues were slower than those of the matched HC group and consumed more time in the order of loss, win, and draw as the outcome conditions (Fig. 2). The calculated reaction time, which was presumably associated with the speed of cognitive processing, was significantly prolonged in PD patients as compared with the HC group only when instructed to lose in response to auditory cues (Fig. 3). The reaction errors were always more numerous in the PD group than in the HC group, with significantly higher error rates when asked to lose (Fig. 4).

Although a decline of the executive function in the PD patients who participated in this study was observed with the TMT [8-10], no significant differences were observed between the PD and HC groups in the other neuropsychological examinations (MMSE, WAIS-R, and WF). Another significant difference was found between the two groups in GDS15. These results are consistent with the previous report of Uekermann et al. [30] that PD patients exhibit executive dysfunction and a depressed mood from the early stages of the disease, although they have good intellectual function.

In the choice reaction task, or the paper-rock-scissors game with the precued signal, the performances of the two groups varied. Both groups exhibited significantly longer reaction times for win than for draw and the longest time for loss against sensory cues (Figs. 2 and 3). In addition, both groups showed significantly higher error rates in reaction to the sensory cues when requested to lose than when requested to draw, except in the case of the PD group's response to visual cues with auditory distracters (Fig. 4). These results may indicate that in this choice reaction task, the disadvantageous and unusual reaction (loss) required a longer time and induced more numerous errors than the advantageous and habitual one (win). With regard to the selection of a response resulting in advantageous or disadvantageous outcomes, a key process in choice reaction is the establishment of a value system. Several theoretical models have been proposed in this regard. Some models [31,32] concentrate on prediction errors broadcasted by monoaminergic neurons, especially by dopaminergic neurons, and decreased transmission in these is one of the pathophysiological hallmarks of a PD brain.

Since the Japanese people are accustomed to playing this game from their early childhood, the automatic and incorrect "win" response has to be inhibited and substituted with the correct "lose" response when they are asked to lose during the choice reaction task. Therefore, as it requires overriding habitual and well-learned actions, the paradigm used in this study is possibly associated with a stimulus-response compatibility effect. In fact, our data are consistent with the effect of stimulus-response compatibility [33], namely, subjects typically respond more slowly and less accurately in incompatible conditions (the lose condition in our study) than in compatible conditions (win).

Attentional deficits are reported to occur even in the early stages of PD, before the patients exhibit a frontostriatal-type dementia characterized by deficits in information-processing speed and executive function [34]. PD patients without dementia are also known to be impaired in tasks that require them to pay considerable attention to internal cues [11]. Although the PD patients enrolled in this study did not display symptoms of dementia (Table 1), the choice reaction task revealed various differences in the performances of the HC and PD groups. Both groups had significantly longer reaction times for win than for draw and with each of the four types of stimuli, the longest time was for loss ($p < 0.05$). In addition, both groups showed significantly higher error rates with all cues when requested to lose than when requested to draw ($p < 0.05$ or $p < 0.01$), except for the visual cues with auditory distracters in the PD group.

It can be speculated that the complex choice reaction task used here requires much more

attention than does the original paper-rock-scissors game because the rules were modified to override habitual actions. The results in terms of reaction times and error rates were improved for draw than for win or loss; therefore, the amount of attentional load may be less in the draw condition. Our study is consistent with the previous reports of a slowness in simple and choice reaction time tasks [35, 36], and of a cognitive deficit affecting the monitoring of stimulus-response compatibility which may contribute to delayed response in PD [37].

The sensory distracters significantly delayed the reaction for draw in both the HC and PD groups (Fig. 2). In these tasks, the processing of auditory information may not generally be subject to visual distraction due to the slow processing of auditory information in itself. However, in the reaction to auditory cues, a significant delay by visual distracters was observed in the HC group when the subjects were required to lose the game. It appeared that the HC group might be more affected in choice reaction by visual distracters than the PD group, which may indicate lowered attentional capacity for visual information in the PD patients under incompatible conditions. However, when considering the motor dysfunctions in PD, the calculated time lag for loss (L-D time in Table 3A) was significantly reduced (approximately 25%) by the distracters in most responses in both groups, except for the responses to auditory cues in the HC group. This may indicate that the cognitive processing of the sensory information was not interfered with but facilitated by the distracters in the PD patients. In this paradigm, the sensory distracters were provided simultaneously with the target cues after the instructions to respond only to the targets but not the distracters. In other words, the subjects were precued to selectively deploy attention during the task, and their brains might have been placed in a biased attentional state [38]. Therefore, it is possible that the sensory distracters were cross-modally suppressed and served to focus attention in the PD patients. These results suggest that anticipatory biased attention [39] was not impaired in the PD patients, although they often display cognitive slowing [40] and deficits in focused and sustained attention [41].

In our study, in the draw condition, motor reaction times to the visual cues with distracters were 12.8% slower in the HC group and 19.4% slower in the PD group than those for visual cues without distracters. However, these changes were not significant in the response to the auditory cues (Fig. 2). Again, this may indicate lowered attentional capacity for visual information in the PD patients under incompatible conditions.

With regard to the differences in simple draw responses between a single cue and a mixed cue, the reaction time to a visual cue was longer (Fig. 2, $p < 0.05$), while the reaction error rate for an auditory cue was higher (Fig. 4, $p < 0.05$) in both groups. These results suggest that the mixed cues influenced choice reaction. Suteerawattananon et al. [21] reported that cueing by visual stimulation was more effective than a combination of visual and auditory stimuli on the gait cadence and stride length of PD patients. This appears to be consistent with our results, as they employed dual cues; an auditory cue of a metronome beat 25% faster than the subject's fastest gait speed simultaneously with a visual cue of lines at intervals equal to 40% of a subject's height. During their study, however, the subjects might have internally selected one of the dual sensory cues, which differs from our paradigm involving the external pre-selection of the target cue.

In summary, our study suggests that a visual cue has a greater influence on choice reaction than an auditory one and that both reaction times and error rates increase under stimulus-response incompatible conditions with disadvantageous outcomes. These changes in the performances might dominate in PD rather than in HC. When we consider the rehabilitation of PD patients, these results may help therapists in devising improved training programs. Anticipatory biased attention to visual cues with precedent auditory stimuli may be fruitful in rehabilitation therapy, so that PD patients do not have to inhibit their habitual performances. Further, considerable attention should be paid when PD patients undertake stimulus-response incompatible tasks with disadvantageous outcomes, in order to avoid clinical complications and to improve their QOL. The clinical effects on PD patients have yet to be evaluated.

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Figures legends

Fig. 1. Experimental paradigm

A trial began with the presentation of prime stimuli, and buzzers rang twice per second. One second after the second buzzer, one of the four types of sensory cues was presented in random sequence. The PC waited for the subject's reaction for two seconds following which the next trial commenced.

Fig. 2. Reaction times for draw, win, and loss with the four types of sensory cues in the HC and PD groups

D, draw; W, win; L, loss; V, visual cue; A, auditory cue; V+, visual cue with auditory distracter; A+, auditory cue with visual distracter. $*p < 0.05$, $**p < 0.01$ in chi-square statistic.

Fig. 3. Calculated reaction time

The calculated reaction time by subtracting the reaction time (RT) in the draw condition from those in the win or loss condition was presumed to be the time for cognitive processing; it is presented with the four types of sensory cues in the HC and PD groups. W-D, RT for win minus RT for draw; L-D, RT for loss minus RT for draw; V, visual cue; A, auditory cue; V+, visual cue with auditory distracter; A+, auditory cue with visual distracter: $**p < 0.01$.

Fig. 4. Error rates for draw, win, and loss with the four types of sensory cues in the HC and

PD groups.

D, draw; W, win; L, loss; V, visual cue; A, auditory cue; V+, visual cue with auditory distracter; A+, auditory cue with visual distracter: $^*p < 0.05$, $^{**}p < 0.01$.

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TABLE 1. Demographic characteristics of healthy control (HC) and the patients with Parkinson's disease (PD).

	HC (n = 20)	PD (n = 30)	p
Gender (male : Female)	6 : 14	14 : 16	0.24
Age	58.6 ± 7.2 (40 - 68)	60.4 ± 9.8 (40 - 74)	0.39
Education	12.7 ± 2.3 (9 - 18)	13.5 ± 3.2 (9 - 22)	0.42
Handedness	all right-handed	all right-handed	
MMSE	29.9 ± 0.5 (28 - 30)	29.7 ± 0.5 (29 - 30)	0.19
WAIS (Total IQ)	114.3 ± 9.5 (100 - 133)	113.6 ± 13.3 (86 - 134)	0.94
WAIS (Verbal IQ)	114.4 ± 11.6 (100 - 134)	115.0 ± 16.5 (67 - 148)	0.63
WAIS (Performance IQ)	115.5 ± 10.2 (95 - 130)	106.1 ± 19.3 (31 - 127)	0.06
SWF (animals)	16.6 ± 3.3 (7 - 20)	16.6 ± 4.3 (7 - 25)	0.94
PWF ("ka")	13.5 ± 3.9 (11 - 24)	11.9 ± 3.8 (5 - 19)	0.19
TMT-A	31.8 ± 9.6 (16.2 - 49.5)	46.3 ± 16.0 (21.7 - 75.6)	0.002
TMT-B	72.3 ± 12.6 (51.4 - 96.0)	104.1 ± 43.5 (50.3 - 232.3)	0.02
GDS15	3.4 ± 1.8 (1 - 8)	6.8 ± 4.0 (1 - 14)	0.001

Mean ± SD (range)

n, number of subjects; HC, healthy controls; PD, Parkinson's disease; n, number of subjects; MMSE, mini-mental state examination; WAIS, Wechsler adult intelligence scale; IQ, intelligence quotient; SWF, semantic word fluency; PWF, phonemic word fluency; TMT, trail making test; GDS15, fifteen-item geriatric depression scale; p, P-value by student's t test

TABLE 2. Disease severity of the patients with Parkinson's disease.

Hoehn and Yahr (stage)	1 n = 1	2 n = 20	3 n = 9	Total 2.3 ± 0.5 (1 - 3)
Duration (years)	5	6.8 ± 12.2 (3 - 13)	15 ± 9.6 (5 - 35)	9.2 ± 6.6 (3 - 35)
UPDRS (on phase)	5	27.6 ± 11.9 (7 - 49)	35.6 ± 9.0 (27 - 55)	29.2 ± 12.2 (5 - 55)
UPDRS (off phase)	5	35.3 ± 11.3 (13 - 54)	43.6 ± 10.8 (30 - 63)	36.8 ± 12.9 (5 - 63)
L-Dopa dose (mg/day) (n = 1)		600		600
L-Dopa dose (mg/day) + DCI (n = 29)	500	335.5 ± 130.5 (150 - 700)	388.9 ± 102.4 (300 - 600)	357.8 ± 123.8 (150 - 700)

Mean ± SD (range)

n, number of subjects; UPDRS, unified Parkinson's disease rating scale; DCI, dopa decarboxylase inhibitor

TABLE 3. Effect of distracter

A) Calculated reaction times (second)

outcome	cue	HC (n = 20)	PD (n = 30)
W-D	V	0.29 ± 0.14	0.27 ± 0.14
	V+	0.24 ± 0.09	0.29 ± 0.24
	A	0.44 ± 0.12	0.54 ± 0.29
	A+	0.47 ± 0.20	0.48 ± 0.19
L-D	V	0.59 ± 0.15**	0.57 ± 0.19**
	V+	0.44 ± 0.20	0.43 ± 0.24
	A	0.64 ± 0.21*	0.98 ± 0.31**
	A+	0.79 ± 0.20	0.72 ± 0.28

B) Error rates (%)

outcome	cue	HC (n = 20)	PD (n = 30)
Draw	V	0.003 ± 0.01	0.050 ± 0.09
	V+	0.003 ± 0.01	0.080 ± 0.13
	A	0*	0.007 ± 0.02**
	A+	0.010 ± 0.03	0.050 ± 0.07
Win	V	0.04 ± 0.05	0.05 ± 0.07**
	V+	0.03 ± 0.05	0.13 ± 0.14
	A	0.06 ± 0.08	0.10 ± 0.09*
	A+	0.07 ± 0.07	0.14 ± 0.13
Loss	V	0.07 ± 0.10	0.18 ± 0.16
	V+	0.05 ± 0.07	0.16 ± 0.18
	A	0.09 ± 0.07*	0.21 ± 0.15**
	A+	0.13 ± 0.10	0.31 ± 0.21

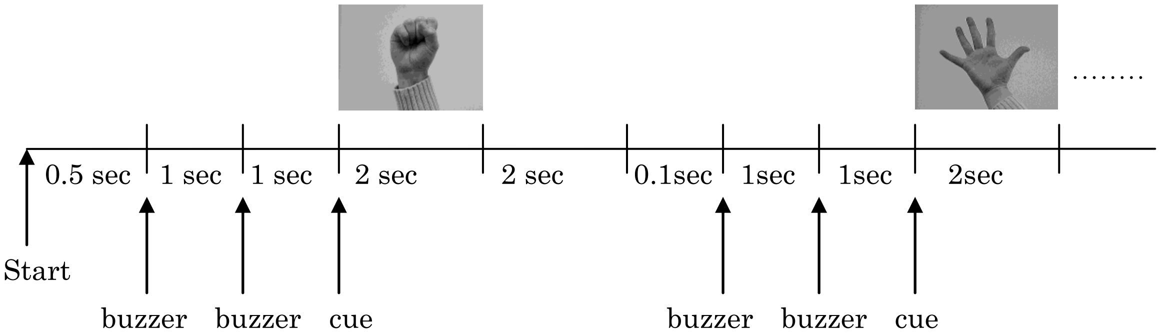
Mean ± SD

HC, healthy controls; PD, patients with Parkinson's disease; n, number of subjects; V, simple visual cues; V+, visual cues with auditory distracters; A, simple auditory cues; A+, auditory cues with visual distracters; W-D, presumed time lag in mental processing for win; L-D, presumed time lag in mental processing for loss

*$p < 0.05$, **$p < 0.01$ for difference from response to cue without distracter by Wilcoxon signed rank test

Fig. 1. Paradigms used in this study

In case of visual cue



types of sensory cues	first series			second series			third series		
visual cue	win	loss	draw	loss	draw	win	draw	loss	win
auditory cue	draw	win	loss	win	draw	loss	win	loss	draw
visual cue with the distracter of an auditory cue	win	draw	loss	win	loss	draw	loss	win	draw
auditory cue with the distracter of a visual cue	loss	draw	win	draw	loss	win	draw	win	loss

One block consisted of 6 trials.

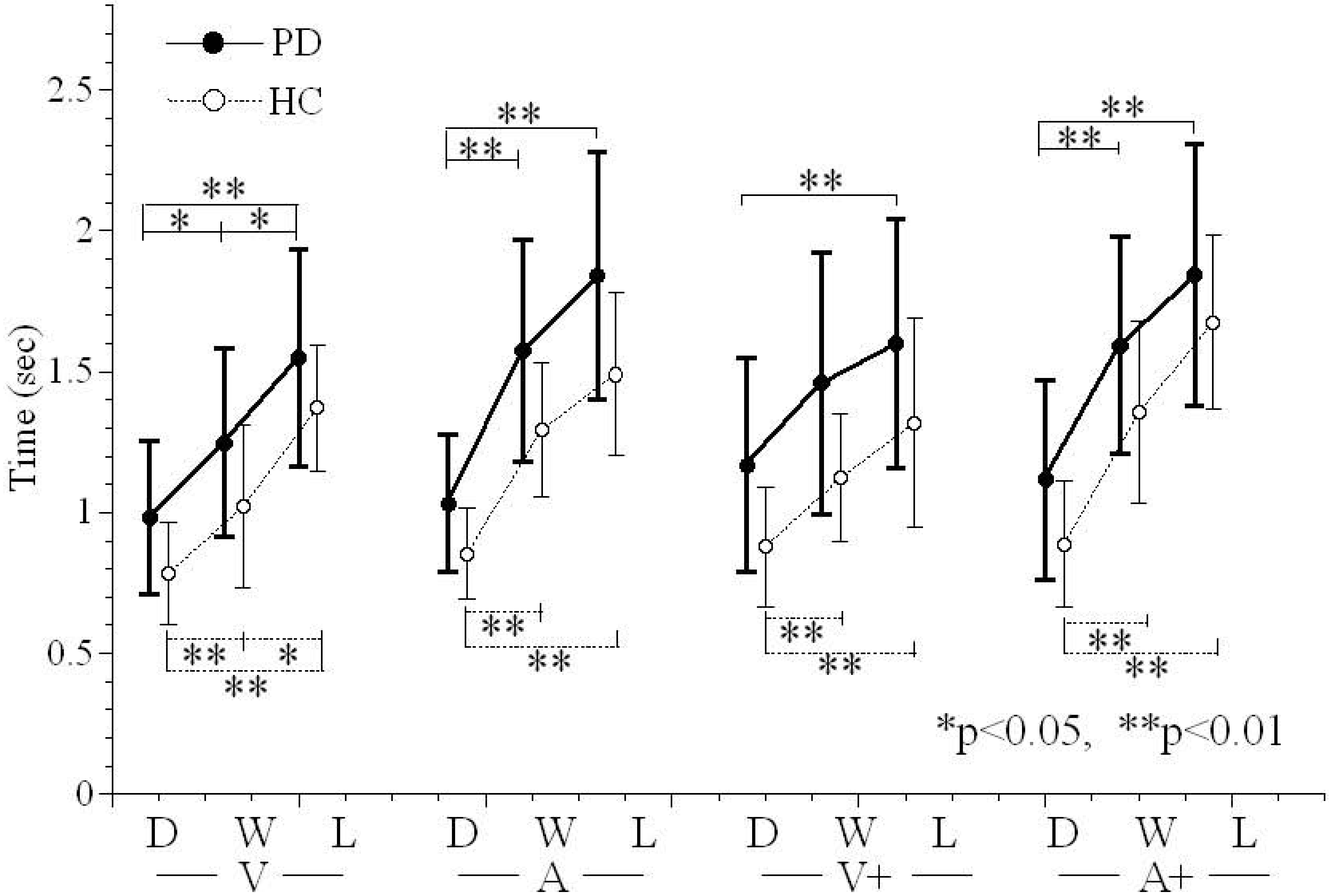


Fig.2

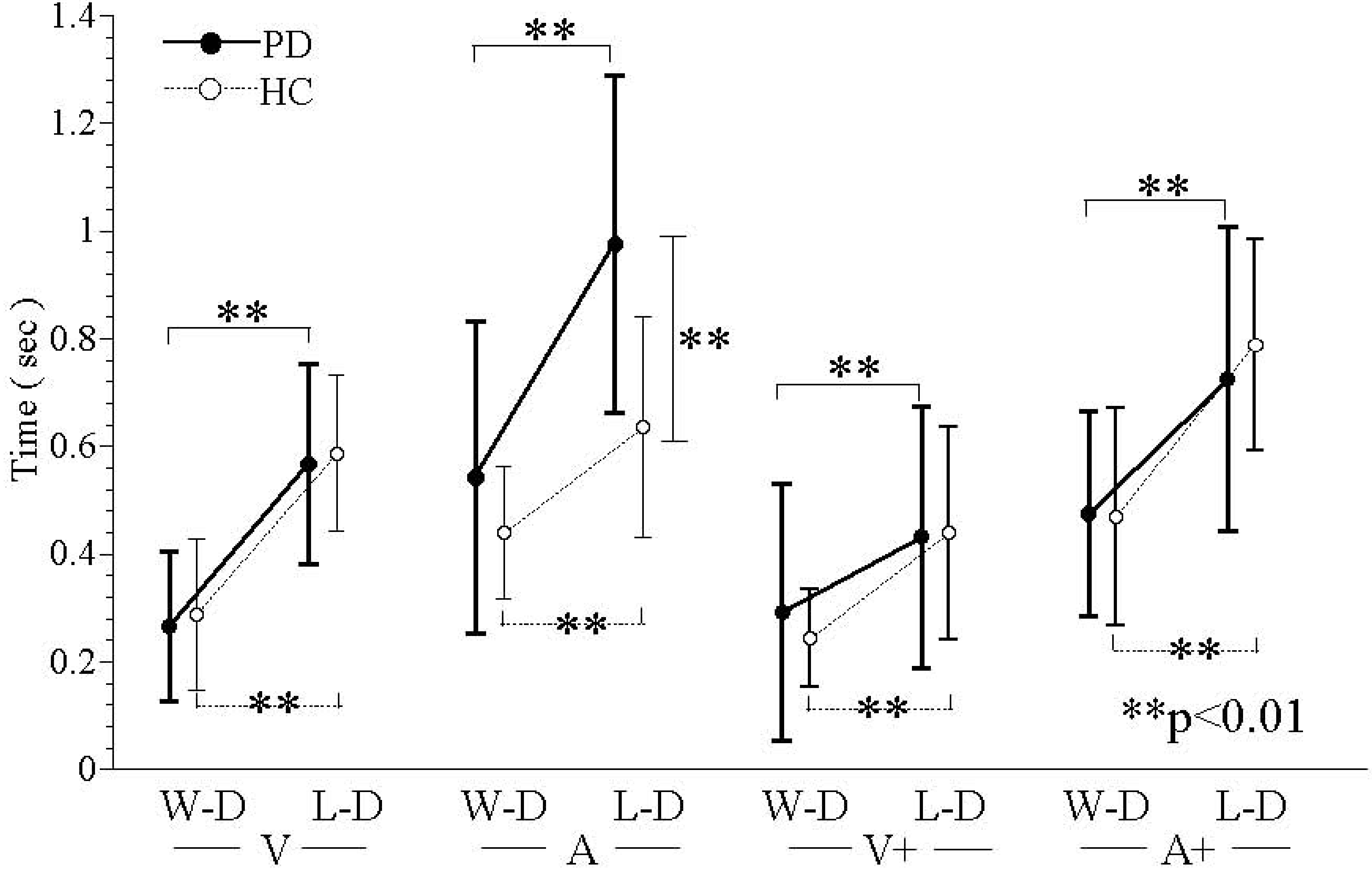


Fig.3.

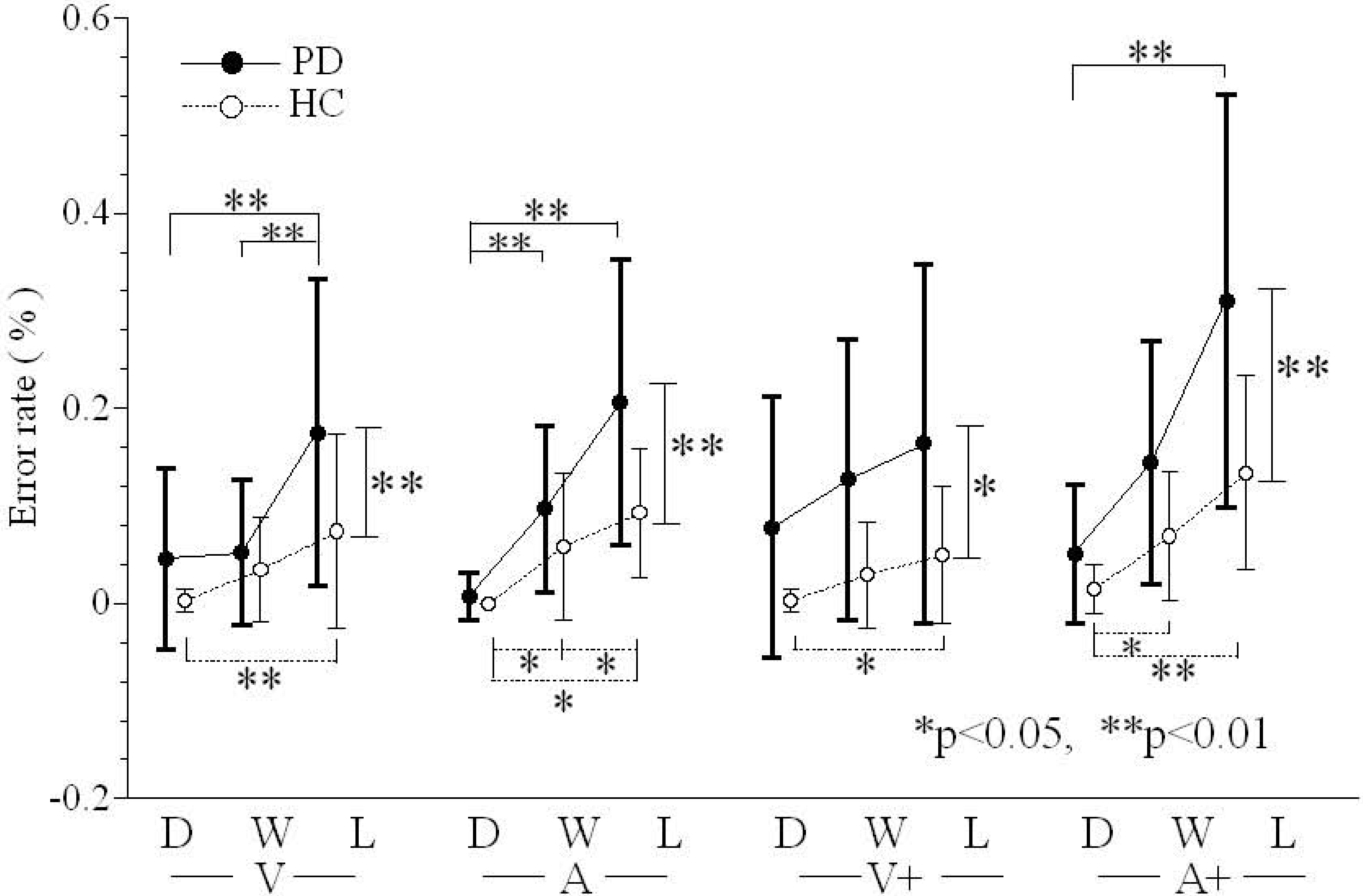


Fig.4.