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RESEARCH ARTICLE

Stopwatch training improves cognitive functions in patients with Parkinson's disease

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Abstract

Parkinson's disease (PD) impairs various cognitive functions, including time perception. Dysfunctional time perception in PD is poorly understood, and no study has investigated the rehabilitation of time perception in patients with PD. We aimed to induce the recovery of time perception in PD patients and investigated the potential relationship between recovery and cognitive functions/domains other than time perception. Sixty patients with PD (27 females) and 20 healthy controls (10 females) were recruited. The participants underwent a feedback training protocol for 4 weeks to improve the accuracy of subjective spatial distance or time duration using a ruler or stopwatch, respectively. They participated in three tests at weekly intervals, each comprising 10 types of cognitive tasks and assessments. After duration feedback training for 1 month, performance on the Go/No-go task, Stroop task, and impulsivity assessment improved in patients with PD, while no effect was observed after distance feedback training. Additionally, the effect of training on duration production correlated with extended reaction time and improved accuracy in the Go/No-go and Stroop tasks. These findings suggest that time perception is functionally linked to inhibitory systems. If the feedback training protocol can modulate and maintain time perception, it may improve various cognitive/psychiatric functions in patients with PD. It may also be useful in the treatment of diseases other than PD that cause dysfunctions in temporal processing.

KEYWORDS

feedback training, impulsivity, Parkinson's disease, response inhibition, time perception

1 | INTRODUCTION

Estimation of the passage of time is an important function to prepare for and predict an action to or smoothly communicate with others. The sensory systems corresponding to time perception remain unknown; consequently, the processing of time perception is considered to be extremely complex and thought to be accomplished by a wide neural network including regions such as the prefrontal cortex, striatum, hippocampus, nucleus subthalamicus, and cerebellum (Buhusi & Meck, 2005; Shi et al., 2013). Distortion of time perception has been reported in a number of diseases, including epilepsy (Drane et al., 1999), depression (Thones & Oberfeld, 2015),

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schizophrenia (Su et al., 2015), and attention-deficit hyperactivity disorder (Suarez et al., 2013). In particular, studies on Parkinson's disease (PD) have shown that patients with PD tend to underestimate time intervals or mispredict timing (Honma et al., 2016; Smith et al., 2007), and that the administration of a dopamine agonist leads to a shift toward normal produced time duration (Lange et al., 1995; Pastor et al., 1992; Smith et al., 2007). These findings suggest that a striatum-centered network plays a functional role in time perception (Buhusi & Meck, 2005; Koch et al., 2008), although the underlying mechanisms remain unclear.

It has been shown that patients with PD have decreased levels of dopamine (Haber, 2014) and that they may further develop disorders related to striatal proteins such as the presynaptic dopamine transporter (DaT), which is responsible for the incorporation and transmission of dopamine components (Vaughan & Foster, 2013). Furthermore, PD affects various executive functions. For example, cognitive dysfunctions are observed in response inhibition (Baglio et al., 2011; Picazio et al., 2018), task-switching (Langston & Virmani, 2018), working memory (Moustafa et al., 2013), reasoning (Mole et al., 2020), language (Magee et al., 2019), and others. In addition, some patients present with risks of psychiatric disorders such as depression (Schrag et al., 2007), anxiety (Rutten et al., 2017), impulsivity (Kubera et al., 2019), and apathy (Costa et al., 2018). While it is known that deficits of dopamine and/or DaT are commonly involved in these dysfunctions in association with cortical neurodegeneration (Huntley & Benson, 2020), it is unclear a functional relationship between the cognitive functions in PD.

A previous study demonstrated that although PD patients who underestimate a duration were instantly modified by a training protocol to learn the accurate duration, the effect of training disappeared within a few minutes (Honma et al., 2018). This indicates that an abnormal speed of subjective time in PD is robust. However, the training was occasional and brief; a more frequent and more prolonged training may alter and consolidate the time perception in PD. In this study, we investigated whether recovery from the distortion in time perception is possible and examined whether the recovery affects other cognitive functions in patients with PD.

Executive function is a general control mechanism that coordinates various cognitive processes (Diamond, 2013), and time perception is considered to be one of them. Time perception may be related to various cognitive processes in executive function. If so, improved time perception may be associated with improvements in other functions, including psychiatric diseases. Specifically, for response inhibition and task-switching functions, incorrect responses (e.g., pressing a wrong button impulsively) may be reduced if we succeed in decelerating time perception in PD. Slow time perception may allow some leeway to stop the erroneous action. Furthermore, an improved function of response inhibition may be related to making decisions, which may, in turn, be associated with impulsivity disorder. Some studies, in fact, have reported that response inhibition is related to impulsive behavior (Bari & Robbins, 2013; Brown et al., 2015; Horn et al., 2003). Daily continuation of transient behavioral inhibition may produce impulsivity inhibition in mental functions. PD leads to shorter evaluation of duration, and PD patients may have faster button-press decisions than those without PD. In this study, we tested whether the remediation of time perception, obtained by providing feedback training of slowing time perception for a month, affects other cognitive functions and predispositions to psychiatric diseases in patients with PD showing characteristics of a fast internal clock and shortened duration perception.

Significance

Many previous studies have reported a variety of cognitive impairments in individuals with Parkinson's disease (PD). In this study, we investigated the effects of time or spatial estimation training protocols on cognitive task performance in patients with PD. We found that a recovery of time estimation performance was associated with improvements in inhibitory responses. Our findings provide evidence for future application of time perception modification techniques for PD rehabilitation.

2 | MATERIALS AND METHODS

2.1 | Participants

This study was approved by the ethics committee of Showa University Hospital and conducted according to the principles of the Declaration of Helsinki (clinical trial identifier number: 4192). The sample size was determined by the effect size reported in previous studies related to cognition and learning (Honma et al., 2017, 2018). All participants provided written informed consent. Of the 160 patients who met the diagnostic criteria of the PD Society Brain Bank (Daniel & Lees, 1993), clinical neurologists selected 60 patients (27 females, mean age: 70.41 years) with no brain abnormalities and sufficient scores in two cognitive assessment batteries (Supporting Information Table S1): the Mini-Mental Status Examination (MMSE; recruitment criterion was ≥ 26 points) (Folstein et al., 1975) and the Montreal Cognitive Assessment (MoCA; recruitment criterion was ≥ 26 points) (Rossetti et al., 2011). They randomly assigned the patients to three groups in the order in which they were registered (groups A, B, and C) (Supporting Information Figure S1). The selected patients with PD showed no brain abnormalities, including atrophy or vascular lesion, on fluid attenuated inversion recovery MRI (Supporting Information Figure S2). We also selected 20 healthy controls (group D) (10 females, mean age: 70.80) with no brain abnormalities and sufficient criteria in both MMSE and MoCA, from 22 age-matching persons.

All participants were right-hand dominant. PD severity was measured using the Unified PD Rating Scale (UPDRS) part-III, Hoehn–Yahr scale, and disease duration. All patients were using a dopamine agonist (carbidopa/levodopa–equivalent daily dose), which had no

influence on DaT imaging (Kagi et al., 2010), and participated in tests and training in the *On* condition, in which medicine was being administered. DaT scanning used ioflupane (^{123}I-FP-CIT), a radio-iodinated cocaine analog (Tatsch & Poepperl, 2013). It has a high affinity for the DaT protein expressed on presynaptic nerve endings in the striatum originating from projections of dopaminergic neurons from the substantia nigra. The radioactive agent bound to DaT was expressed using a specific binding ratio: the ratio of the radiations in the striatum to those in the whole brain, as calculated by the Bolt method (Tossici-Bolt et al., 2006) (Supporting Information Figure S3). DaT imaging was conducted within 3 months before behavioral tests. DaT imaging data showed no differences among groups A, B, and C (Table 1).

2.2 | Experimental design

Tests were conducted three times at 4 weeks intervals (Figure 1). Each test involved production of a 10 s duration and 10 cm distance (Honma et al., 2017), Go/No-go (Aron, Robbins, et al., 2004; Filevich et al., 2012), Stroop (Langston & Virmani, 2018; Peterson et al., 1999), N-back (Honma et al., 2010; Moustafa et al., 2013), and simple reaction tasks. In addition, depression (Richter et al., 1998; Schrag et al., 2007), anxiety (Newham et al., 2012; Rutten et al., 2017), impulsivity (Kubera et al., 2019; Patton et al., 1995), and motor examination (Unified PD Rating Scale: UPDRS part-III) (Martinez-Martin et al., 1994) were examined. Feedback training of duration or distance lasted for 4 weeks (28 days in a row) in groups A and B (Figure 1). Group D of age-matched healthy controls received no training. Groups A and B underwent duration and distance feedback training according to a crossover design. Group C received no training throughout the experiment. A follow-up was conducted a month after the experiment.

2.3 | Behavioral tasks in the test session

2.3.1 | Production tasks for duration and distance

For the test sessions, the participants were asked to wait for 10 s without a temporal cue in the duration production task. They were instructed to press the start button of a stopwatch, and after estimating a 10 s interval without glancing at the panel of the stopwatch, were instructed to press the stop button. In the distance production task, the participants were asked to draw a 10 cm long line in the left-to-right direction on white paper lacking any distance measuring cue. The same trial was repeated thrice per test, and the average was treated as one sample.

2.3.2 | Go/No-go task

An auditory Go/No-go task was employed to elucidate response inhibition. An auditory Go task was used to determine simple properties of a motor response skill as a control (Video S1). Two trial blocks of the No-go task and the Go task were run in a randomized order to minimize potential biases in task performance caused by inter-block interferences. Each trial block was separated by a 30-s inter-block interval. Each trial block consisted of 10 trials with changing inter-trial intervals (ITIs: average, 750 ms; range, 500–1,000 ms). Participants listened to a sequence of 20 individual 50-ms tone stimuli at 70 decibels in a trial block via headphones. The sequence consisted of 15 low-pitched tone stimuli (75%) of 1,000-Hz frequency and 5 high-pitched tone stimuli (25%) of 1,200-Hz frequency. Participants had to respond to all tones by pressing a space button as quickly and accurately as possible in the Go trial blocks. In the No-go trial blocks, participants had to respond to low-pitched tones by pressing a button as quickly and accurately as

TABLE 1 Participant details

	Group A (Parkinson's disease)	Group B (Parkinson's disease)	Group C (Parkinson's disease)	Group D (Healthy control)
Age	70.35 (4.17)	70.30 (5.34)	70.75 (6.21)	70.80 (6.27)
Sex				
Female	8	10	9	10
Male	12	10	11	10
Hand dominance				
Right	20	20	20	20
Left	0	0	0	0
MMSE	27.85 (1.60)	28.15 (1.57)	27.90 (1.65)	28.55 (1.52)
MoCA	27.25 (1.24)	27.25 (1.71)	26.95 (1.23)	27.50 (1.23)
Hoehn–Yahr stage	3.05 (0.85)	2.90 (0.79)	2.95 (0.83)	–
Disease duration (years)	7.70 (4.91)	7.75 (4.80)	7.15 (4.72)	–
DaT imaging	0.47 (1.19)	0.55 (1.24)	0.35 (1.09)	–

Note: DaT imaging, Data on Dopamine Transporter scan in striatum; MMSE, Mini-Mental State Examination (max: 30); MoCA, Montreal Cognitive Assessment (max: 30). The standard deviations are shown in parentheses.

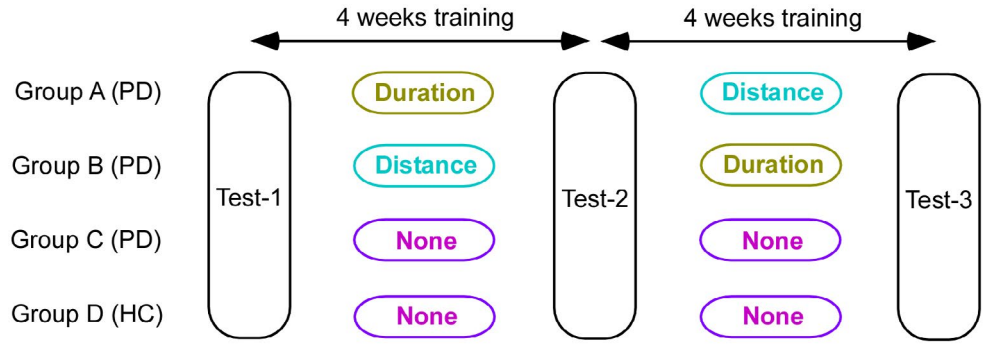

FIGURE 1 Experimental design. To examine the effect of feedback training, tests were conducted three times at 4 weeks intervals. Each test involved productions of 10 s duration and 10 cm distance, Stroop, N-back, Go/No-go, and simple reaction tasks. In addition, assessments of impulsivity, depression, anxiety, and UPDRS part-III scores were conducted. Feedback training for duration or distance lasted for 4 weeks. Sixty patients with Parkinson's disease were assigned to three groups (groups A, B, and C) in this randomized controlled trial. Groups A and B underwent duration and distance feedback trainings according to a crossover design. Group C and D were no-training groups. Group D consisted of 20 age-matched healthy controls. HC, healthy controls; PD, patients with Parkinson's disease [Color figure can be viewed at wileyonlinelibrary.com]

possible, but they had to withhold a response to high-pitched tones. Thus, 20 and 15 responses were obtained in the Go and No-go tasks, respectively, in each trial block. Reaction times and accuracy rates were calculated in each block and session. Responses made after 500 ms from the offset of tone stimuli were considered faults.

2.3.3 | Stroop task

The Stroop task was used to assess interference effects; participants were asked to name the color of the ink in which a word was written while ignoring the meaning of the word (Video S2). Reaction time (from letter presentation to button press) to name the ink color was slower when text is incongruent (the word "RED" in blue ink; incongruent Stroop task) than when it is congruent with the color ("RED" in red ink; congruent Stroop task). The letter was presented until a response was obtained. We performed 20 trials with a combination of congruent and incongruent tests. The trial order was randomized.

2.3.4 | N-back task

The present study used a visual N-back working memory task with two separate levels. Four circles appeared abreast on a scene. One of the circles was orange in color and the rest were aqua in color. Participants were instructed to press a button corresponding to the location of the orange circle. For the 0-back task (low level), they were asked to determine the location of the orange circle currently displayed. For the 2-back task (high level), they were asked to determine the location of the orange circle displayed two scenes prior, and to simultaneously remember the location of the orange circle currently displayed for two scenes after (Video S3). A 1,500-ms baseline period preceded the tasks. The scenes were presented in a randomized order for 300 ms with a 1,700-ms inter-stimulus interval. Each level of the task was run in blocks of 12 + N stimuli and was conducted two times; thus, 24 responses were obtained at each load level. The inter-trial interval was set at 2,500 ms. From the performance data recorded, average reaction time and accuracy rate were determined. The trial order was randomized.

2.3.5 | Simple reaction task

For the simple reaction task, participants were instructed to press a response button using their dominant hand whenever a circled figure appeared on the computer screen. We performed three trials. The inter-trial interval was set at 5,000 ms.

2.4 | Clinical assessments in the test session

2.4.1 | Impulsivity

The Barratt Impulsiveness Scale (BIS-11) is a questionnaire designed to assess the personality/behavioral construct of impulsiveness. The current version is composed of 30 items describing common impulsive or non-impulsive (for reverse scored items) behaviors and preferences. Items are scored on a 4-point scale (rarely/never = 1; occasionally = 2; often = 3; almost always/always = 4). The total score is calculated as the sum of all item scores and ranges from 30 to 120.

2.4.2 | Depression

The BDI involves a series of questions developed to measure the intensity, severity, and depth of depression in patients with psychiatric diagnoses. It consists of 21 items that measure symptoms of depression, such as pessimism, sense of failure, guilt, self-dislike, suicidal ideas, insomnia, and weight loss. The total score is calculated as the sum of all item scores, and ranges from 0 to 63.

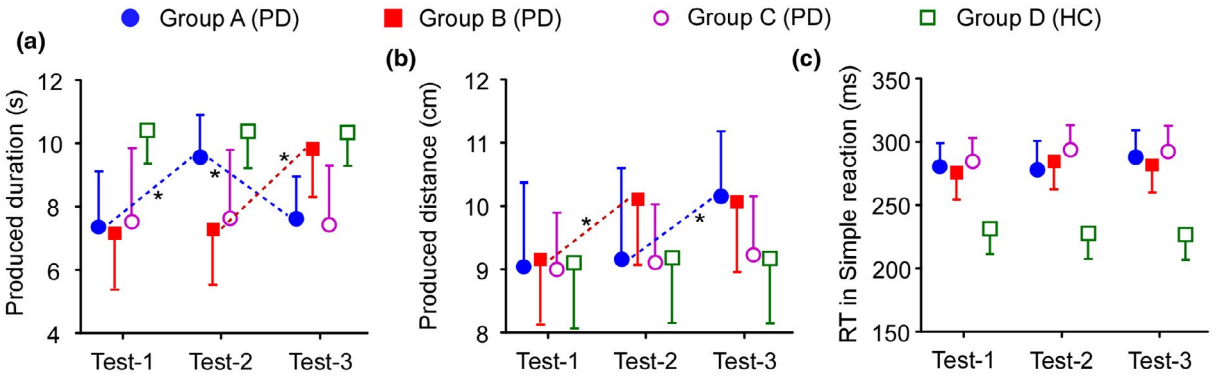

FIGURE 2 Effects of feedback training on duration/distance productions and simple reaction in each group. (a) Produced durations of groups A, B, and C were shorter than that of group D in test-1. The duration was similar between groups A and D in test-2 and between groups B and D in test-3. (b) Produced distances of all groups showed no differences in test-1. The distance was similar between groups B and D in test-2 and between groups A and D in test-3. (c) Reaction time (RT) of groups A, B, and C were longer than that of group D in test-1. The RTs in the simple reaction task showed negligible changes throughout the tests. Error bars show standard deviation. Asterisks mean significant differences ($p < 0.05$). HC, healthy controls; PD = patients with Parkinson's disease [Color figure can be viewed at wileyonlinelibrary.com]

2.4.3 | Anxiety

The STAI separately measures state anxiety, which reflects the transitory emotional state or condition of the subject characterized by subjective, consciously perceived feelings of tension and apprehension, and trait anxiety, which reflects relatively stable individual differences in anxiety proneness and refers to a general tendency to respond with anxiety to perceived threats in the environment. Both the state and trait sections of this questionnaire comprised 20 questions, with total scores in each section ranging from 20 to 80.

2.5 | Behavioral tasks in the training session

For the training sessions, all trials were accompanied by feedback. In the duration training, the participants were instructed to press the start button of a digital stopwatch, and after estimating a 9 or 11 s interval without glancing at the panel of stopwatch, were instructed to press the stop button. They confirmed the duration by looking at the panel and wrote down the results on a record sheet by hand. In the distance training, the participants first drew a line, which they estimated to be 9 or 11 cm in length, on white paper lacking length measuring cues; the length of the line was subsequently measured with a ruler and the results were recorded on a record sheet by hand. The ruler cue involved drawing a ruler with the scale in millimeters, with its maximum value set at 15 cm. The same trial was repeated 10 times daily for 4 weeks. The training sessions were conducted at home without supervision.

2.6 | Statistical analyses

For the present experimental design, a linear mixed model suitable for repeated measurements was used as a statistical method. The method modeled individual differences in data over time for each individual as a random effect. For the initial test (test-1), one-way ANOVA was used for default states of the patients. All tests were two-tailed. Results are shown as mean ± standard deviation (*SD*). Statistical significance was defined as adjusted $p < 0.05$. Pearson's correlation coefficients were used to examine associations between training effect on the duration production task and effects on improved cognitive tasks and assessment scores. The FDR was applied to the correlation analyses. SPSS 22.0 for Windows (IBM, Inc., Chicago, IL) was used for the statistical analyses.

3 | RESULTS

3.1 | Cognitive and psychiatric disorders in patients with PD

In test-1, one-way ANOVA revealed that duration production was shorter in groups A, B, and C compared to group D ($F_{3,79} = 17.787$, $p < 0.0001$, Figure 2a). Distance production showed no significant differences between groups in the test-1 (Figure 2b). Accuracy rates of the No-go ($F_{3,79} = 7.698$, $p < 0.0001$, Figure 3a), incongruent Stroop ($F_{3,79} = 21.385$, $p < 0.0001$, Figure 3b), and 2-back ($F_{3,79} = 14.674$, $p < 0.0001$, Figure 3c) tasks were lower in the PD groups than in the healthy control group, while those of the Go, congruent Stroop, and 0-back tasks showed no differences between the healthy control and the three groups with PD. Reaction time in the PD groups was longer than that in the healthy control group in the No-go ($F_{3,79} = 9.133$, $p < 0.0001$, Figure 3d), incongruent Stroop ($F_{3,79} = 6.110$, $p < 0.0001$, Figure 3e), 2-back ($F_{3,79} = 3.099$, $p < 0.05$, Figure 3f), simple reaction ($F_{3,79} = 9.378$, $p < 0.0001$, Figure 2c), Go ($F_{3,79} = 4.516$, $p < 0.01$, Figure 4a), congruent Stroop ($F_{3,79} = 4.333$, $p < 0.01$, Figure 4b), and 0-back tasks ($F_{3,79} = 8.934$, $p < 0.0001$, Figure 4c). Furthermore, the

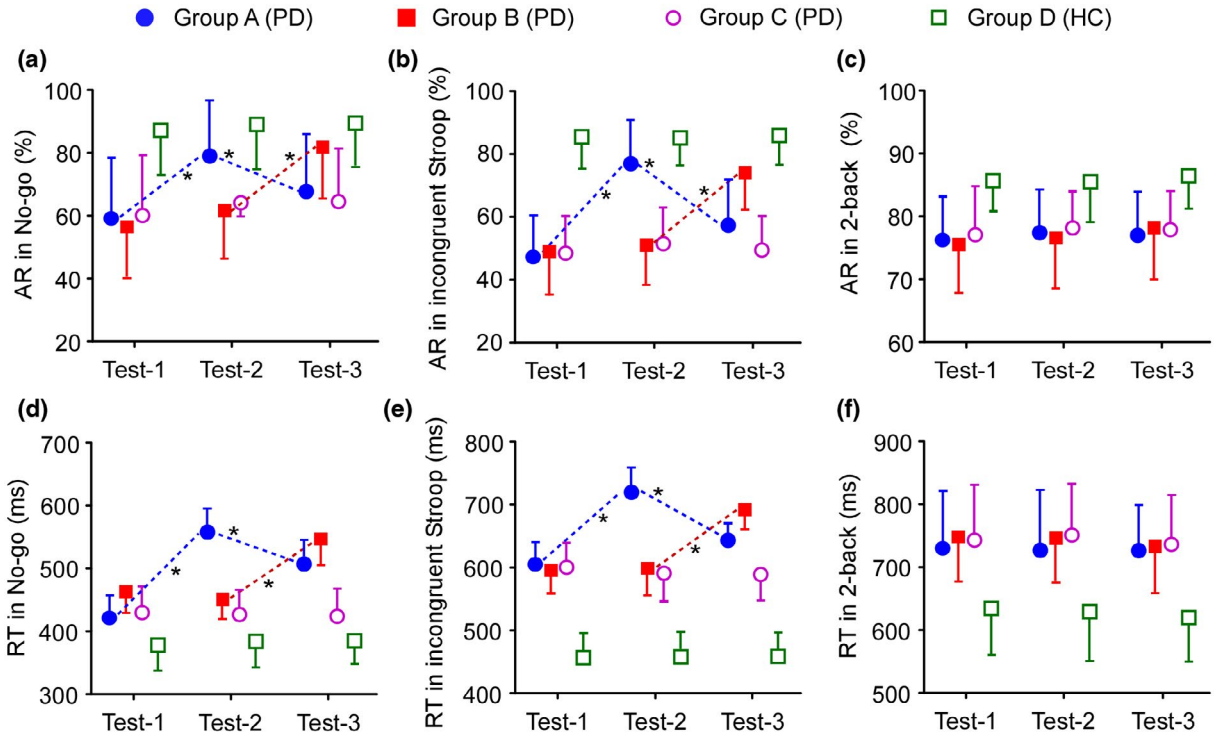

FIGURE 3 Effects of feedback training on performance in the No-go, incongruent Stroop, and 2-back tasks in each group. In test-1, accuracy rates (ARs) of groups A, B, and C were lower than that of group D with regard to (a) No-go, (b) incongruent Stroop, and (c) 2-back tasks. The AR increased in test-2 in group A and in test-3 in group B with regard to (a) No-go and (b) incongruent Stroop tasks. (c) The AR in the 2-back task showed a negligible change throughout the tests. In test-1, reaction times (RTs) of groups A, B, and C were shorter than that of group D in the (d) No-go, (e) incongruent Stroop, and (f) 2-back tasks. RTs were prolonged in test-2 in group A and in test-3 in group B in the (d) No-go and (e) incongruent Stroop tasks. (f) The RT in the 2-back task showed negligible changes throughout the tests. Error bars show standard deviation. Asterisks mean significant differences ($p < 0.05$). HC, healthy controls; PD, patients with Parkinson's disease [Color figure can be viewed at wileyonlinelibrary.com]

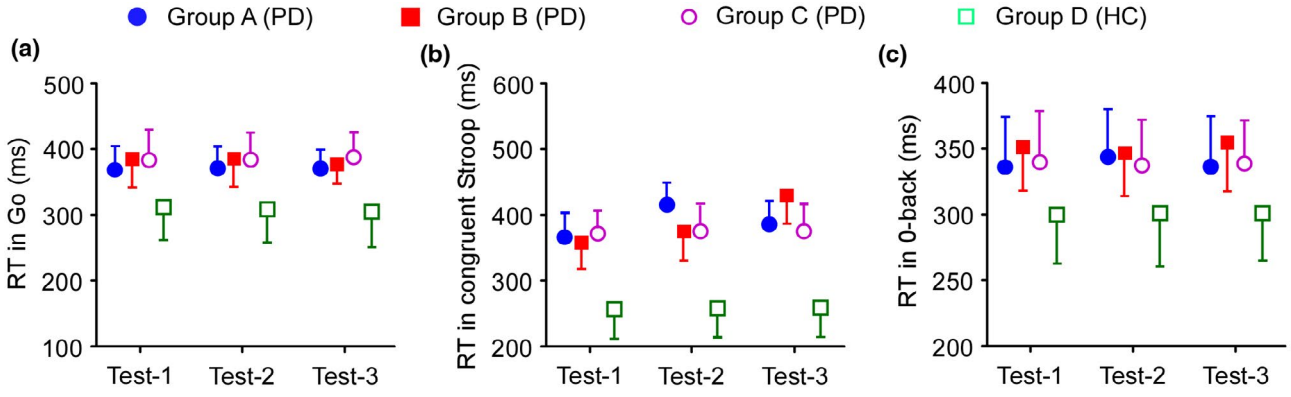

FIGURE 4 Effects of feedback training on performance in the Go, congruent Stroop, and 0-back tasks in each group. Reaction times (RTs) in groups A, B, and C were shorter than that in group D in test-1 with regard to (a) Go, (b) congruent Stroop, and (c) 0-back. The RTs s showed negligible change throughout the tests. Error bars show standard deviation. HC, healthy controls; PD, patients with Parkinson's disease [Color figure can be viewed at wileyonlinelibrary.com]

three groups with PD showed higher predisposition to psychiatric disorders, such as impulsivity ($F_{3,79} = 12.156$, $p < 0.0001$, Figure 5a), depression ($F_{3,79} = 22.348$, $p < 0.0001$, Figure 5b), and anxiety (trait: $F_{3,79} = 5.314$, $p < 0.005$, Figure 5c; state: $F_{3,79} = 6.630$, $p < 0.0001$, Figure 5d), than the healthy control group.

3.2 | Duration feedback training improves performance on Go/No-go and Stroop tasks

In tests-2 and −3, LMM showed that distance feedback training affected distance production alone (Figure 2b), and duration

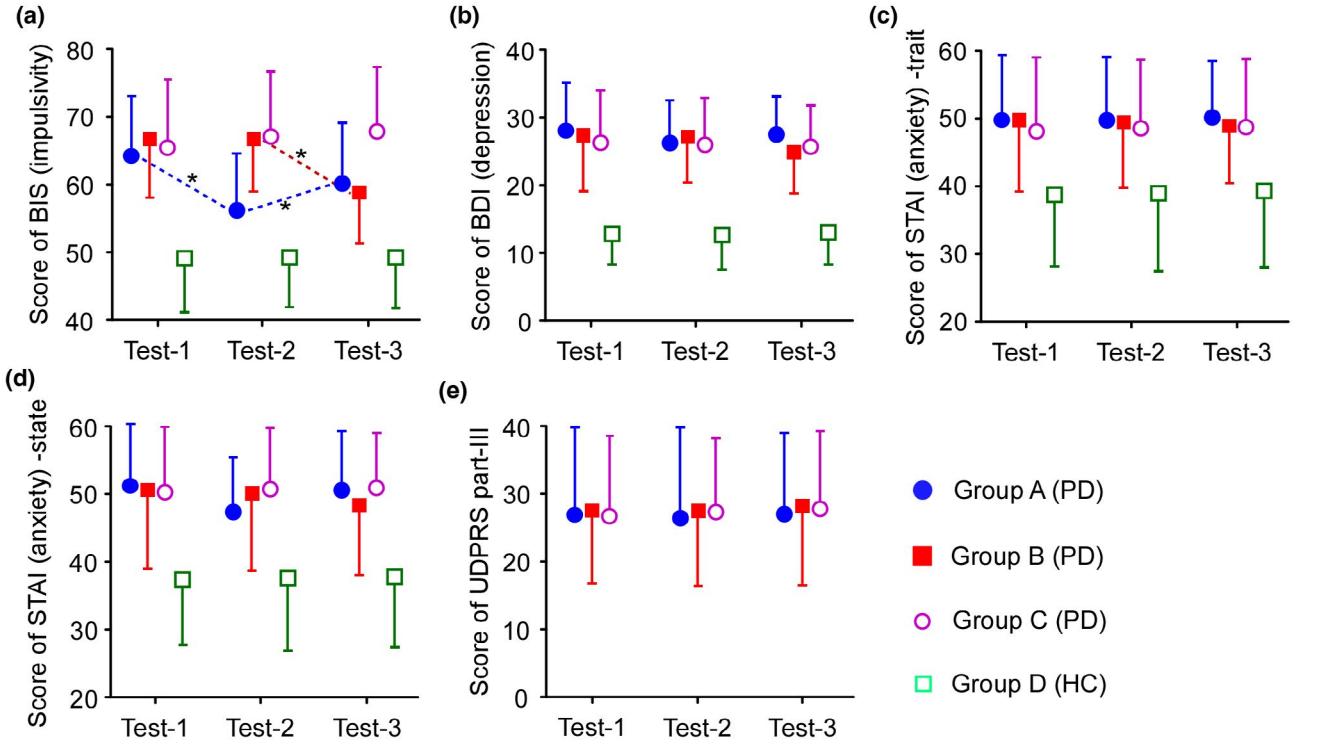

FIGURE 5 Effects of feedback training on clinical assessment scores in each group. In test-1, clinical scores of groups A, B, and C were lower than those of group D with regard to (a) BIS, (b) BDI, (c) STAI-trait, and (d) STAI-state. (a) The BIS score improved in test-2 in group A and in test-3 in group B. (b) BDI, (c) STAI-trait, and (d) STAI-state scores showed negligible changes throughout the tests. (e) The UPDRS part-III score showed negligible changes throughout the tests. Error bars show standard deviation. Asterisks mean significant differences ($p < 0.05$). HC, healthy controls; PD, patients with Parkinson's disease [Color figure can be viewed at wileyonlinelibrary.com]

training affected duration production alone (Figure 2a, post hoc tests: respectively $p < 0.0001$) (Supporting Information Table S2 for details). In the No-go tasks, accuracy rate increased (Figure 3a, respectively $p < 0.0001$) and reaction time was prolonged in test-2 of group A and test-3 of group B (Figure 3d, respectively $p < 0.0001$) (Supporting Information Table S3 for details). In the incongruent Stroop tasks, accuracy rate increased (Figure 3b, respectively $p < 0.0001$) and reaction time was prolonged in test-2 of group A and test-3 of group B (Figure 3e, respectively $p < 0.0001$) (Supporting Information Table S4 for details). In the 2-back task, feedback training had no effect on either accuracy rate (Figure 3c) or reaction time (Figure 3f) (Supporting Information Table S5 for details). Reaction time in the simple reaction task in all groups remained unchanged throughout the tests (Figure 2c) (Supporting Information Table S2 for details). Groups C and D maintained their performance throughout the tests.

3.3 | Duration feedback training improves impulsivity disorder assessment

LMM showed that the BIS scores decreased in test-2 of group A and test-3 of group B (Figure 5a, post hoc tests: respectively $p < 0.0001$). In the depression and anxiety assessments, feedback training showed no effect (Figure 5b–d). The UPDRS part-III scores exhibited no differences between groups (Figure 5e). Groups C and D maintained their performance throughout the tests (Supporting Information Table S6 for details).

3.4 | Correlation of duration training effects between duration production and other indexes

We conducted correlation analysis for the confirmed training effect of duration feedback in 40 patients with PD. The training effect was evaluated by subtracting the values before training with that after training. Specifically, the training effect was evaluated by subtracting test-1 from test-2 in group A, and by subtracting test-2 from test-3 in group B. The false discovery rate (FDR) was applied to the results of the correlation analyses (p value on FDR = 0.001). The training effect on duration production correlated with that on the No-go task for reaction time ($r = 0.639$; $p < 0.0001$; Figure 6a) and accuracy rate ($r = 0.619$; $p < 0.0001$; Figure 6b). Similarly, the training effect on duration production correlated with that on the incongruent Stroop task for reaction time ($r = 0.594$; $p < 0.0001$; Figure 6c) and accuracy rate ($r = 0.581$; $p < 0.0001$; Figure 6d). In contrast, the training effect on the score in the BIS correlated marginally with the training effect on duration production ($r = -0.414$; $p = 0.008$; Figure 6e).

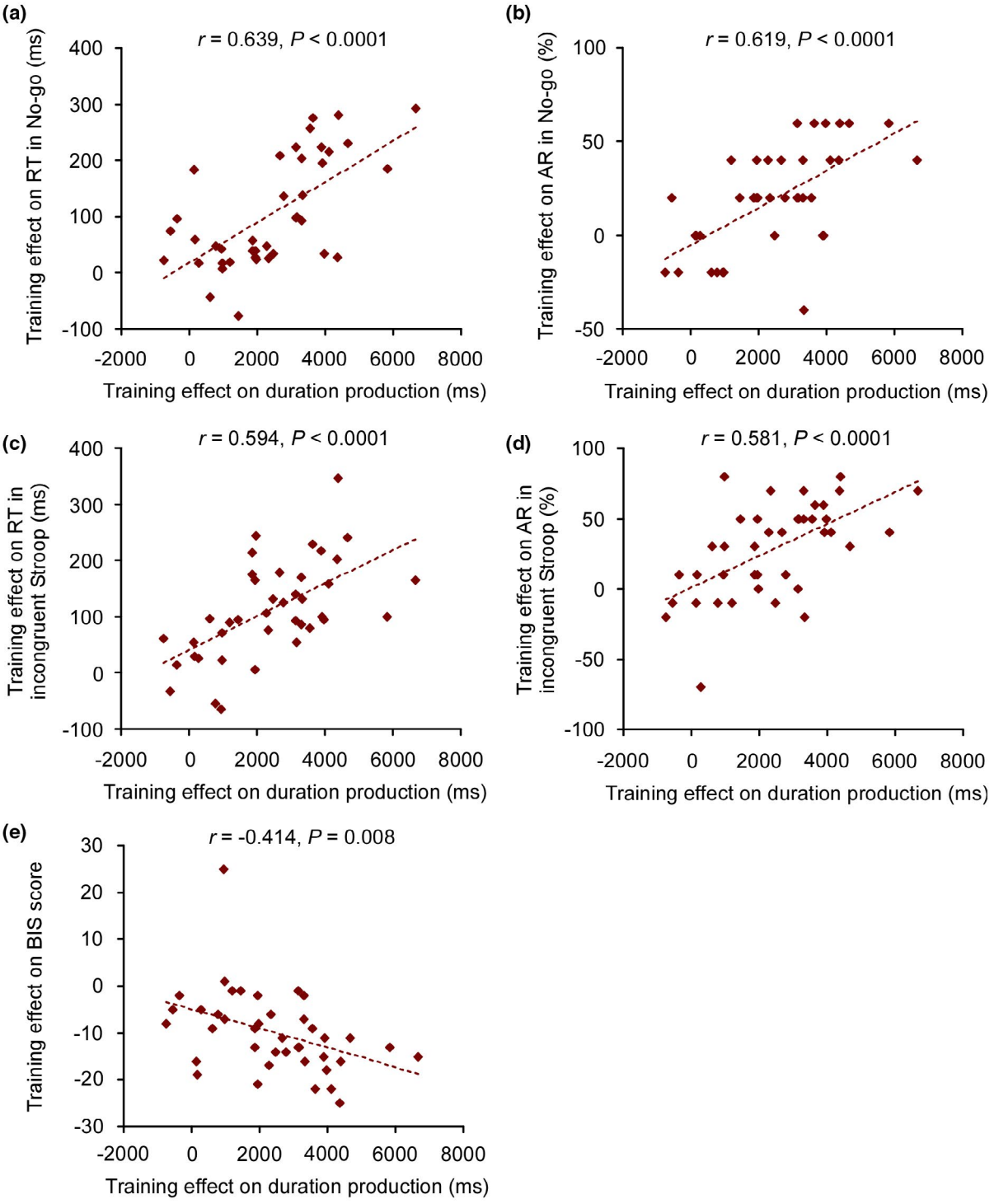

FIGURE 6 Correlation between duration production and duration training effect. The training effect on duration production correlated with (a) reaction time (RT) and (b) accuracy rate (AR) in the No-go tasks. The training effect correlated with (c) RT and (d) AR in the incongruent Stroop task. In contrast, (e) the training effect on BIS score correlated marginally with that on duration production. Samples included groups A and B. The line indicates the best-fit linear regression. *r* and *p* indicate Pearson's correlation coefficient and the uncorrected *p* value, respectively [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

This study aimed to induce the recovery of time perception in PD patients, and investigated the potential relationship between recovery and cognitive functions/domains other than time perception. In patients with PD who exhibited the characteristics of shortened duration production, duration feedback training was found to improve the duration production. The modulated subjective time estimation affected accuracy and reaction time in the No-go and incongruent Stroop tasks. The modulation also affected the

index of predisposition to impulsivity. Additionally, we found that the effect fades within 1 month. In contrast, distance feedback training had little effect on other indices.

Duration feedback training successfully improved accuracy and extended reaction time in the No-go and incongruent Stroop tasks, but not in the 2-back task in patients with PD. The effects of training manifested as an accuracy/reaction time trade-off. The results of the trade-off suggest that patients became able to act accurately in exchange for a delay in response. It is possible that this delay in response was caused by a slowing of the flow of subjective time due to duration training. Furthermore, the training effect on duration task correlated with the training effect on the No-go and incongruent Stroop tasks, indicating that the improvement in duration training, rather than participation in the duration training overall, affects improvement on cognitive tasks. The duration training for a month might have modulated the perception of the passage of subjective time and consolidate a new sense for estimating subjective time intervals. This finding suggests that the slowing down of subjective time improves the function of response inhibition but not of working memory systems.

In the current study, simple reaction time and UPDRS part-III scores (for motor examination) remained unchanged throughout all the tests, suggesting that feedback training had little effect on motor systems. Although the activity of the prefrontal cortex is common to the three executive tasks (Brown et al., 2015; Carlson et al., 1998; Horn et al., 2003), it is unlikely that duration training affected only the prefrontal cortex within duration-related regions, because no effect was observed in the N-back task. Alternatively, it may exhibit a characteristic response on the inferior frontal gyrus and anterior cingulate cortex in the Go/No-go and Stroop tasks (Brown et al., 2015; Horn et al., 2003). These regions are related to an inhibition of behavior (Aron, Monsell, et al., 2004; Aron & Poldrack, 2006), and therefore, duration training may improve the activity of these regions. In contrast, because distance feedback training did not affect the accuracy and reaction time in any of the tasks, the training may not affect these regions; therefore, it is not conducive to the slowing of time perception and inhibition of behavior. New time perception may be consolidated by modulating the regions associated with time processing.

Duration feedback training also affected an index of impulsivity. Because the training had no effect on depression and anxiety, slowing of subjective time may be associated with improvement of impulsivity. Studies suggest that response inhibition is related to impulsive behavior (Bari & Robbins, 2013; Horn et al., 2003; Verbruggen et al., 2019). Although the inability of the prefrontal cortex in controlling the activity of the amygdala is common in depression (Groenewold et al., 2013), anxiety (Mochcovitch et al., 2014), and impulsivity (Ludwig et al., 2015), some patients with PD with impulsive control disorders exhibit an abnormality in the frontal, cingulate, temporo-parietal, and occipital regions (Kubera et al., 2019). Duration training may improve the functional abnormalities of these regions.

While cognitive improvements via training of the same cognitive domain or via exercise have been reported (Audiffren & André, 2019; Northey et al., 2018), there are no studies in our knowledge focusing on the effects of training on time perception. This study showed the possibility of a new rehabilitative effect using time perception training in PD patients showing temporal dysfunction. The novelty of this finding is that modulated time perception re-establishes functions related to inhibition of actions and mental functions without specific training for the latter. The current study suggests that a time perception system is functionally linked to inhibition systems. Although some aspects of the mechanisms underlying impulsivity remain unclear, remediation of time perception may be associated with behavioral control. Furthermore, the daily continuation of the transient behavioral inhibition may produce an impulsivity inhibition in mental functions.

The current study has several limitations. First, the training sessions were conducted at home without supervision, thereby we cannot deny the probability that some participants did not obey our training procedure correctly. While there were handwritten records for the values of duration and distance, experiments in full surveillance would be ideal. Second, the experiment was not controlled for bradykinesia in PD patients. Bradykinesia could affect all trials requiring button presses, although the influence may have a similar impact on the same tasks. A voice reaction may be less biased in the current experiment with PD. Third, the fading within a month of the duration training effect could be a limitation of the present finding. The number of days and/or the amount of training may be a limit for this study. It is necessary to evaluate the amount of training required to maintain the effect.

In conclusion, we showed that stopwatch training affects time estimation as well as inhibition functions, while distance training has no effect on the functional connectivity in patients with PD. We believe that our results represent a landmark discovery, although they will need replication from other cohorts. If time perception can be modulated and maintained by the feedback training, it may improve various cognitive/psychiatric functions in patients with PD. Additionally, it may be used for treating diseases other than PD that also cause dysfunctions in temporal processing.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

CONFLICT OF INTEREST

No conflicting interests exist.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*, M.H.; *Methodology*, M.H., M.K.,

and K.O.; *Investigation*, M.H., H.M., T.K., A.F., A.S., and M.K.; *Formal Analysis*, M.H., Y.Y., Y.T., Y.M., and M.I.; *Resources*, M.K. and K.O.; *Writing – Original Draft*, M.H.; *Writing – Review & Editing*, M.H., M.H., Y.Y., and K.O.; *Visualization*, M.H.; *Supervision*, M.K.; *Funding Acquisition*, H.M. and M.K.; *Project Administration*, K.O.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study and custom code used for analyses are available from the corresponding authors upon reasonable request. The data have not been made publicly available as they contain information that could compromise the privacy of the research participants.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

TABLE S1 Clinical features of selected and excluded patients

TABLE S2 Statistics list for duration/distance production and simple reaction

TABLE S3 Statistics list for Go/No-go task

TABLE S4 Statistics list for Stroop task

TABLE S5 ANOVA list for N-back task

TABLE S6 ANOVA list for clinical assessments

FIGURE S1 From 160 patients with PD, we selected 60 patients with no signs of dementia on the basis of MRI, MMSE, and MoCA. We assigned them to 3 groups (groups A, B, and C) in randomized controlled trials. We also selected 20 Healthy Controls with no neurological disease history and no signs of dementia from 22 age-matched persons (group D)

FIGURE S2 Representative images of fluid attenuated inversion recovery MRI on coronal view. (a) Sample of healthy person (female, 78 years). (b) Sample of person with suspected dementia (female, 84 years). The hippocampus is atrophied and the inferior horn of the lateral ventricle is enlarged

FIGURE S3 Representative images of dopamine transporter scan on coronal view. (a) Sample of normal control (male, 75 years). (b) Sample of patient with Parkinson's disease (male, 73 years, Hoehn-Yahr stage: 3, UPDRS-III score: 35, Disease duration: 6 years). The imaging show little accumulation of radiation in the striatum. The numbers indicate binding radiation counts per pixel

VIDEO S1 A trial of Nogo task. Participants had to respond to low-pitched tones by pressing a button as quickly and accurately as possible, but they had to withhold a response to high-pitched tones.

VIDEO S2 A trial of incongruent Stroop task. Participants were asked to name the color of the ink in which a word is written while ignoring the meaning of the word.

VIDEO S3 A trial of 2-back task. Participants were asked to answer the location of orange circle two scenes before, and to simultaneously remember the location of orange circle at hand for two scenes after.

Transparent Science Questionnaire for Authors

Transparent Peer Review Report

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