Neuropsychologia 102 (2017) 61–69

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

# Spatial distortion related to time compression during spatiotemporal production in Parkinson's disease

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ARTICLE INFO

*Keywords:*
Spatiotemporal production
Parkinson's disease
Aging
Striatal dopamine transporter

ABSTRACT

To produce coordinated manual actions within specific space and time, their relationship must be properly dealt with in a sensorimotor system. This study examined how such a coordination system might be impaired in normal aging and in Parkinson's disease (PD). Using a tablet device, young participants, elderly participants, and patients with PD were tested for concurrent production of distance and duration as well as single production of distance or duration alone. Results were analyzed in relation to deficiency of presynaptic dopamine transporter (DaT) in the striatum. We observed different patterns of impairment between normal aging and PD. Elderly participants exhibited duration overproduction when they had to produce distance and duration concurrently, but were normal in single production of either distance or duration. In contrast, PD patients exhibited normal distance production and marked underproduction of duration when either distance or duration was produced alone, but both duration and distance were underproduced when they were concurrently produced. These findings suggest that aging yields impaired performances in both elderly people and PD patients, but that temporal underproduction in PD patients entrains spatial production as if the distance to be produced were made consistent with their duration underproduction. We also observed that striatal DaT deficit was correlated with the extent of duration underproduction in PD patients. The deficit may be associated with the severe time compression and the entrainment during spatiotemporal production in PD patients.

## 1. Introduction

Comprehension and production of distance and duration are essential for coordinated action control; without them, it would be virtually impossible to move an object to a certain location at certain timing without any sensory cue to location or time. Manually produced distance and duration are also important tools for information sharing and nonverbal communications with others in social activities. What mechanisms underlie such spatiotemporal production? Space and time are known as closely coupled psychological dimensions, as demonstrated by psychophysical (Morrone et al., 2005; Frassinetti et al., 2009; Cai and Connell, 2015), neuropsychological (Cappelletti et al., 2009), and neuroimaging studies (Bonato et al., 2012). Classical studies have also documented that spatial and temporal dimensions are interrelated in various contexts, such as time influencing space perception (the tau effect; Helson, 1930) and space influencing time perception (the kappa effect; Cohen et al., 1953). Studies on the neural basis of space perception have put emphasis on the connections from the visual to parietal cortex (PC) and then to prefrontal cortex (PFC) (Quintana and Fuster, 1993; Chafee and Goldman-Rakic, 1998), whereas time perception may involve striatal networks interconnected with the hippocampus, PC, and PFC (Buhusi and Meck, 2005); the PC, PFC, and their combination may play an important role in spatiotemporal integration (Oliveri et al., 2009). Some researchers have also proposed "a theory of magnitude" which states that space, time, and number are represented in equivalent formats and processed in a common analog magnitude system implemented in the PC (Walsh, 2003; Bueti and Walsh, 2009). What remains to be elucidated is the way these internally represented spatial and temporal values are expressed by human motor control such as hand movement.

To examine this, we measured performance of concurrent production of space and time in a single action by asking participants to make horizontal movement of a hand for a certain travelling size and for a certain time interval, hereafter called "distance" and "duration"

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http://dx.doi.org/10.1016/j.neuropsychologia.2017.06.004
Received 19 December 2016; Received in revised form 3 June 2017; Accepted 6 June 2017
Available online 07 June 2017
0028-3932/ 

respectively, and compared the performance of this task with that of single production of distance or duration. If each dimension is processed separately, the motor outputs for all tasks should be similar. Conversely, they should differ if the computations for the two dimensions compete for common cognitive resources during the concurrent productions, as seen in behavioral performances in dual tasks in general (Hartley, 2001; Pashler, 1994). In such cases, spatial and temporal productions can interact in various ways; for example, the production of one dimension may exhibit a greater dispersion whereas the production of the other dimension is relatively unaffected. However, the motor outputs would be effectively similar between the concurrent and single tasks for healthy young people, given that the tasks are simple enough for them to execute concurrently with a negligible effect of resource competition. In contrast, age-related decline may make the effect of resource competition more explicit and thereby impair the concurrent productions of distance and duration. Therefore, comparison of results between young and elderly may elicit identifiable features of spatiotemporal production.

To examine whether conditions affecting time production also affects space production in such a cognitively challenging situation of concurrent productions, we attempted to test concurrent production in patients with conditions that are known to affect time production. Some neurological diseases accompany disordered temporal processing, and this is particularly true for Parkinson's disease (PD), which is marked by difficulties in both comprehension and production of time (Allman and Meck, 2012; Piras et al., 2014). Patients with PD have decreased levels of dopamine (DA) (Haber, 2014) and may further develop disorders related to striatal proteins such as presynaptic dopamine transporter (DaT), which is responsible for the incorporation and transmission of DA components (Vaughan and Foster, 2013). Patients with PD tend to underestimate time intervals (Lange et al., 1995; Smith et al., 2007), and administration of a DA agonist leads to a shift toward normal in produced duration (Pastor et al., 1992), indicating that DA levels are associated with time perception. Furthermore, these characteristics suggest that the basal ganglia are involved in temporal processing (Koch et al., 2008; Torta et al., 2010). On the other hand, distance production has not been tested in patients with PD. We predicted that PD patients would accurately produce distance but would underproduce duration in the single production task, as has been reported previously (Allman and Meck, 2012). What prediction could be made for the concurrent production task? If the computations for productions of space and time are independent of each other with a negligible effect of resource competition, patients would correctly produce distance but underproduce duration. Conversely, if spatial and temporal processes do interact with each other under the condition of resource competition, both distance and duration would differ between single and concurrent production tasks. The concurrent production in patients exhibiting disordered mental time may thus shed light on the underlying mechanism of spatiotemporal processing.

Productions of distance and duration in concurrent production task could be generally less accurate than those in single tasks for both the elderly participants and PD patients, since aging per se would potentially impair performances requiring sensorimotor coordination (Salthouse, 1996; Hartley, 2001). Studies of spatiotemporal comprehension have revealed that temporal representation more heavily depend on spatial representation, than vice versa (Boroditsky, 2000; Casasanto et al., 2010). If this were also true for spatiotemporal production in normal aging, the spatial aspects of internal information would play a more dominant role than the temporal aspects. For the same reason, in patients with PD, the concurrent production of distance and duration may also be impaired. However, it is possible that disordered temporal processing associated with PD still yields severe time compression even with accurate spatial production.

We conducted behavioral experiments to identify the effects of PD and aging on spatial and temporal productions by contrasting their performances with those for normal controls, and used brain imaging to identify the effects of striatal DaT deficit on manual productions in patients with PD. We also confirmed that, when a spatial and/or temporal cue was visually available during task, all the participants had an ability to understand the task, to follow object movement, and to attend to the cue. Furthermore, since elderly people and PD patients may present cognitive deficits, such as inefficient learning in visual discrimination (Price and Shin, 2009) and motor skills (Vandenbossche et al., 2013; Gobel et al., 2013), we examined whether the participants improved distance and/or duration production after feedback.

## 2. Material and methods

### 2.1. Participants

This study was approved by the ethics committees of Showa University Hospital and of the University of Tokyo and was conducted according to the principles of the Declaration of Helsinki. All participants provided written informed consent. Clinical neurologists recruited 39 patients with PD who met the diagnostic criteria of the Parkinson's Disease Society Brain Bank (Daniel and Lees, 1993), and 19 (mean age = 72.63) of them were selected as the participants of this study as having no signs of dementia as determined by two cognitive assessment batteries, the Mini-Mental Status Examination (MMSE; score > 25) testing individual memory, attention, and language abilities (Folstein et al., 1975), and the Montreal Cognitive Assessment (MoCA; score > 25) testing short-term memory, visuospatial abilities, executive functions, attention, concentration, working memory, and language abilities (Nasreddine et al., 2005). We also recruited 18 elderly controls (EC: mean age = 67.72) and 20 young controls (YC: mean age = 18.45) with no neurological disease history and no signs of dementia (Table 1). The difference in age between EC and PD groups was not significant (unpaired *t*-test: $t_{35} = 1.973$, $P > 0.05$). Handedness was assessed by verbal report from the participants and all of them were very confident that they exclusively used the right hand for writing in daily life. The PDs and ECs showed no brain abnormalities on magnetic resonance imaging with fluid attenuated inversion recovery and diffusion-weighted imaging. PD severity was measured using the Unified Parkinson's Disease Rating Scale (UPDRS) (Martinez-Martin et al., 1994), the Hoehn–Yahr scale, and disease duration. All patients were taking a DA agonist (carbidopa/levodopa equivalent daily dose), which had no influence on DaT imaging (Kägi et al., 2010), and participated in behavioral experiments under the *On* condition under which medicine was being administered.

**Table 1**
Participant details.

| | | YC (n = 20) | EC (n = 18) | PD (n = 19) |
|---|---|---|---|---|
| Age (years) | | 18.45 (0.60) | 67.72 (6.59) | 72.63 (6.91) |
| Sex | | | | |
| | Female | 10 | 9 | 11 |
| | Male | 10 | 9 | 8 |
| Hand dominance | | | | |
| | Right | 20 | 18 | 19 |
| | Left | 0 | 0 | 0 |
| MMSE | | 29.75 (0.44) | 27.67 (0.84) | 27.68 (1.29) |
| MoCA | | 28.65 (0.99) | 27.33 (1.41) | 27.67 (1.23) |
| UPDRS | | – | – | 39.7 (27.59) |
| Hoehn-Yahr stage | | – | – | 2.7 (0.91) |
| PD duration (years) | | – | – | 7.2 (4.65) |

YC: Young controls. EC: Elderly controls. PD: Patients with Parkinson's disease. MMSE: Mini-Mental State Examination. MoCA: Montreal Cognitive Assessment. UPDRS: Unified Parkinson's Disease Rating Scale. The standard deviations are shown in parentheses.

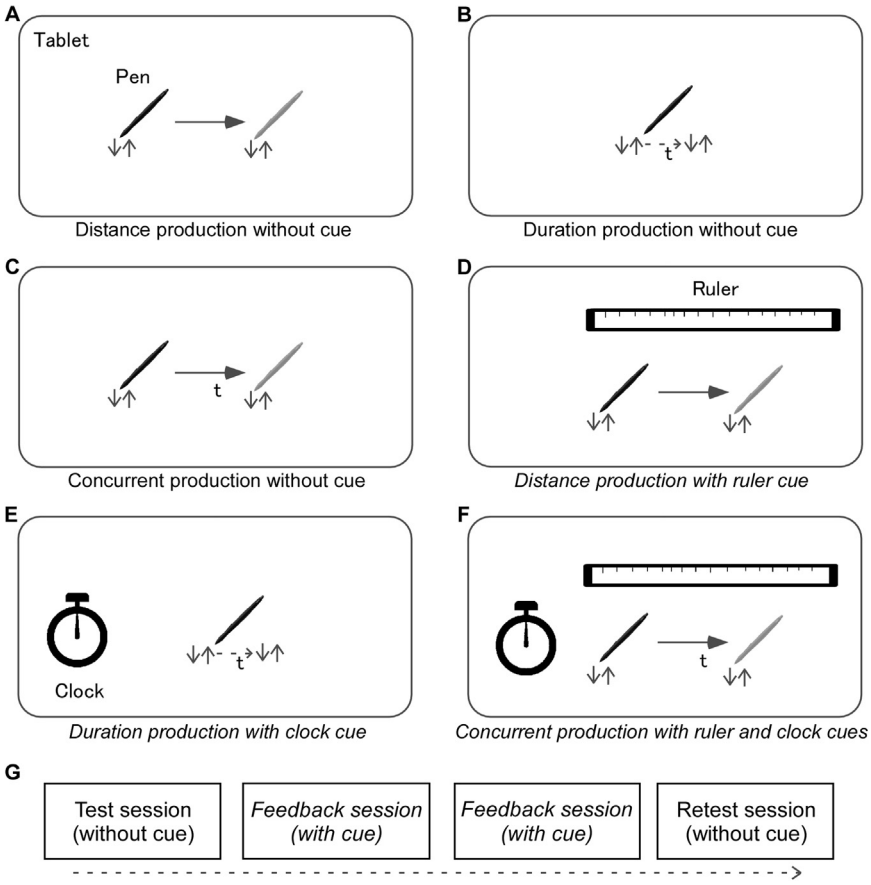


**Fig. 1.** Schematic illustration of trials and experimental flow. (A) The single production task for distance. Distance was produced by moving the pen at any speed for a specified distance. (B) The single production task for duration. Duration was produced by tapping the tablet at the same position when a specified duration was felt to have elapsed. (C) The concurrent production task. Distance and duration were produced by moving the pen for a specified distance, just spending a specified duration. (D) The feedback task for the single distance production. Distance was produced by moving the pen for a specified distance in reference to the position information on the "ruler" cue. (E) The feedback task for the single duration production. Duration was produced by waiting for a specified duration to elapse in reference to the time information on the "clock" cue. (F) The feedback task for concurrent production. Distance and duration were produced by moving the pen with reference to spatial as well as temporal information provided by "ruler" and "clock" cues. (G) Experimental flow.

### 2.2. Behavioral measurements

Participants were asked to produce a specified distance and/or duration with their right hand holding a stylus pen above an electronic tablet (Intuos4 Extra Large, WACOM Corporation, Saitama, Japan; spatial precision ± 0.25 mm, sampling rate 200 points/s, screen size 488 mm × 305 mm, frame size 623 mm × 462 mm). At the beginning of each trial, the distance and/or duration to produce were instructed verbally by the experimenter (Supplementary Video 1). In all conditions, they started each trial when they were ready, tapped the tablet with the pen at the beginning and end of the pen's trajectory, and received no feedback unless specified otherwise. The direction of the pen in the distance production task was from left to right in all trials and the pen trajectory was recorded. In the "single production" task, either distance or duration production was tested. To produce the specified distance, participants were asked to move the pen at a speed as constant as possible over a distance of 10 cm ("S10") or 20 cm ("S20") (Fig. 1A). To produce the specified duration, participants were asked to wait for 10 s ("T10") or 20 s ("T20"), without actually moving the pen (Fig. 1B). In the "concurrent production" task (Fig. 1C), participants were asked to move the pen at a speed as constant as possible for the specified distance, just spending the specified duration. Trials for this task had four combinations: movement for 10 cm in 10 s ("S10T10"), movement for 10 cm in 20 s ("S10T20"), movement for 20 cm in 10 s ("S20T10"), and movement for 20 cm in 20 s ("S20T20"). In the conditions requiring the movement of the pen, participants were asked to move it as constantly as possible and to keep it 5–10 mm above the surface of the tablet (to avoid undesirable occasional contact to the surface due to tremor symptoms that must be especially cared for in patients with PD). The ($x$, $y$) coordinates (trajectory) of the tip of the pen and the tapping actions (contact) were recorded independently. In the "feedback" session, a "ruler" cue (Fig. 1D), a "clock" cue (Fig. 1E), or both cues (Fig. 1F) were provided during each trial. The "clock" cue was a drawing of an analog clock with its dial scales in seconds, with its maximum value set at 60 s, and its second hand in smooth rotation as with a real clock. The "ruler" cue was a drawing of a ruler with its tick scales in millimeters and with its maximum value set at 30 cm.

Supplementary material related to this article can be found online at http://dx.doi.org/10.1016/j.neuropsychologia.2017.06.004.

The experiment consisted of four consecutive sessions: (1) a test session, (2) the first "feedback" session, (3) the second "feedback" session, and (4) a retest session (Fig. 1G). Each of the four sessions consisted of the eight conditions described above ("S10", "S20", "T10", "T20", "S10T10", "S10T20", "S20T10", and "S20T20"). The trial order in each session was randomized. The feedback effect was defined as the difference in performance between the test and retest session. For simplicity, the data for the first and second "feedback" sessions were merged in subsequent analyses as if just one session were carried out.

### 2.3. DaT imaging

DaT scanning used ioflupane ($^{123}$I-FP-CIT), a radio-iodinated cocaine analog (Kagi et al., 2010; Tatsch and Poepper, 2013). It has a high affinity for the DaT protein expressed on presynaptic nerve endings in the striatum originating in projections of dopaminergic neurons from the substantia nigra. The radiation bound to DaT thus reflects the number of dopaminergic neurons in the striatum. Three hours after injection of ioflupane (167 MBq), single photon emission computed tomography imaging was performed using a triple-headed gamma camera (GCA-9300R, Toshiba Medical Systems Corporation, Tokyo, Japan), using fan beam collimators (N2). Ninety projection images were obtained over 360 degrees by rotating each head through 120 degrees, following a circular contour, with the radius of rotation minimized for each patient. The matrix size was 128 × 128, and a magnification factor of 1.00 rendered a pixel size of 1.72 mm. Radiation counts were acquired within a 10% symmetrical energy window centered around

159 keV. Image post-processing was performed using DaTView software (Nihon Medi-Physics, Tokyo, Japan). Raw projections were filtered prior to reconstruction using a Butterworth filter, with a cut-off frequency of 0.76 cycles/cm and order of 4. Trans-axial slices covering the whole brain were reconstructed using OS-EM (four iterations and eight subsets), and the range covered the whole brain with 1 pixel-thick slices. Each striatal volume was set at 11.2 ml in the right and left hemispheres. Radiation bound to DaT was expressed by a specific binding ratio (SBR): the ratio of the radiations in the striatum to those in the whole brain, as calculated using the Bolt method (Tossici-Bolt et al., 2006). The DaT imaging was conducted within 3 months before/after behavioral tests; the chosen criterion of 3 months was well justified by the known dynamics of DaT over months (Ahlskog, 2003).

### 2.4. Statistics

Analysis of variance (ANOVA) and post-hoc *t*-tests were performed for behavioral data and screening scores. Data for the eight conditions ("S10," "S20," "T10," "T20," "S10T10," "S10T20," "S20T10," and "S20T20") were analyzed independently. In addition, the distance and duration in the concurrent production task ("S10T10," "S10T20," "S20T10," and "S20T20") were analyzed separately. To determine the effect of condition, distance production for 10 cm (analysis comparing across the "S10," "S10T10," and "S10T20" conditions hereafter called the "S10-related" combination) and that for 20 cm (analysis comparing across the "S20," "S20T10," and "S20T20" conditions hereafter called the "S20-related" combination) were analyzed separately. Likewise, duration production for 10 s (analysis comparing across the "T10," "S10T10," and "S20T10" conditions hereafter called the "T10-related" combination) and that for 20 s (analysis comparing across the "T20," "S10T20," and "S20T20" conditions hereafter called the "T20-related" combination) were analyzed separately.

## 3. Results

### 3.1. Cognitive assessment

The scores of the cognitive assessments were significantly lower in the EC and PD groups, although all the participants performed above cut-off (score > 25). In the MMSE (Fig. 2A), one-way ANOVA for participant group (YC, EC, and PD groups) confirmed a main effect ($F_{2, 54} = 32.893$, $p < 0.0001$, $\eta^2 = 0.549$). Post-hoc *t*-tests showed that the EC and PD groups exhibited lower scores than the YC group (YC-EC: $t_{36} = 9.695$, adjusted $p < 0.0001$; YC-PD: $t_{37} = 6.741$, adjusted $p < 0.0001$; EC-PD: $t_{35} = 0.049$, adjusted $p = 0.961$). Similarly, in the MoCA (Fig. 2B), the ANOVA confirmed a main effect ($F_{2, 54} = 8.419$, $p < 0.001$, $\eta^2 = 0.238$). Post-hoc *t*-tests showed that the EC and PD groups exhibited lower scores than the YC group (YC-EC: $t_{36} = 3.354$, adjusted $p < 0.005$; YC-PD: $t_{37} = 4.043$, adjusted $p < 0.0001$; EC-PD: $t_{35} = 0.282$, adjusted $p = 0.779$). These results indicate that both the EC and PD groups had similarly compromised cognitive functioning as compared with the YC.

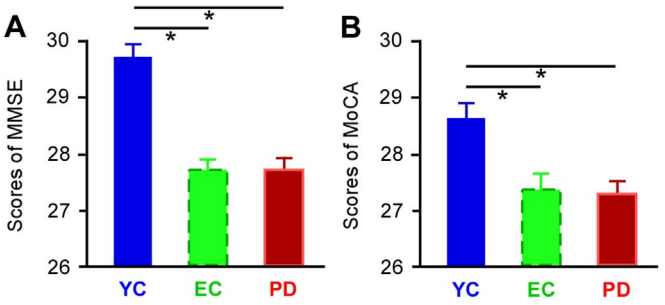


**Fig. 2.** Group comparison in cognitive assessments. (A) MMSE and (B) MoCA scores plotted for the three groups. Asterisks indicate significant differences ($p < 0.05$). Error bars indicate SEM. YC = young control. EC = elderly control. PD = patients with Parkinson's disease.

### 3.2. Behavior measurement

Ten trials (0.55%) out of a total of 1824 (4 sessions × 8 conditions × 57 participants) were excluded from the analysis because of missing data due to technical problems, but it was unlikely that the exclusion systematically biased the results because these trials occurred randomly across conditions and participant groups (1 EC and 1 PD in the "S10" condition of the test session; 1 PD in the "T10" of the test session; 1 EC in the "S10T20" of the test session; 1 EC in the "S20T20" of the test session; 1 EC in the "S10" of the feedback session; 1 PD in the "S20" of the retest session; 1 EC and 1 PD in the "T20" of the test session; 1 EC in the "S10T20" of the retest session). Two-way (3 groups and 3 sessions) ANOVAs were performed for each of the eight conditions (see Supplementary Table 1). In addition, two-way (3 groups and 3 conditions) ANOVAs were performed for each of the four combinations of the test session to determine the difference in performance between the single and concurrent production tasks (see Supplementary Table 2).

#### 3.2.1. Production with feedback

The produced distance and duration did not differ among groups in the feedback session (Fig. 3: middle plots along the horizontal axis in each panel), in which the spatial and/or temporal cue was visually available. Post-hoc *t*-tests confirmed the absence of significant differences in produced distance/duration in all conditions (all adjusted $p > 0.05$). Thus, all participants were able to produce the distance and duration with comparable accuracy in the presence of spatial and/or temporal cues.

#### 3.2.2. Single production

In the test session, the produced *distance* in the "S10" and "S20" conditions did not differ among groups (Fig. 3A and B). For the produced *duration* in the "T10" and "T20" conditions (Fig. 3C and D), however, the PD group yielded a shorter duration compared with the YC and EC groups. An ANOVA confirmed a main effect of group (see Supplementary Table 1 for statistics), and post-hoc *t*-tests showed that the *duration* was shorter in the PD group relative to the YC and EC groups for both the "T10" (PD-YC: $t_{36} = 6.330$, $p < 0.0001$; PD-EC: $t_{34} = 4.478$, $p < 0.0001$) and "T20" (PD-YC: $t_{37} = 6.387$, $p < 0.0001$; PD-EC: $t_{35} = 4.262$, $p < 0.0001$) conditions. In brief, in the single production task, the PD patients produced a normal *distance* but shorter *duration*.

#### 3.2.3. Concurrent production

To evaluate performances of the concurrent production task in the test session in relation to those for the single production task (Supplementary Table 2), separate analyses were made depending on what kind of production was requested (see Methods).

For the PD group, the produced *distance* in the concurrent production task was significantly shorter than that in the single production task (Fig. 4A and B). In the "S10-related" combination analysis (Fig. 4A), the *distances* in the "S10T10" and "S10T20" were shorter than that in the "S10" condition only in the PD group. A two-way ANOVA for group as an across-participant factor and condition ("S10," "S10T10," and "S10T20" conditions) as a within-participant factor revealed main effects of group and condition, as well as their interaction. Multiple comparison tests with Bonferroni correction for group showed that the *distance* for the PD group was shorter than those for the YC (adjusted $p < 0.05$) and EC (adjusted $p < 0.05$) groups. Post-hoc paired *t*-tests within the PD group showed that, compared with the "S10" condition, the *distances* under the "S10T10" ($t_{17} = 2.710$, adjusted $p < 0.05$) and "S10T20" ($t_{17} = 4.293$, adjusted $p < 0.05$) conditions were shorter. The results of *distance* in the "S20-related" combination analysis were essentially the same as above (Fig. 4B): compared with the "S20"

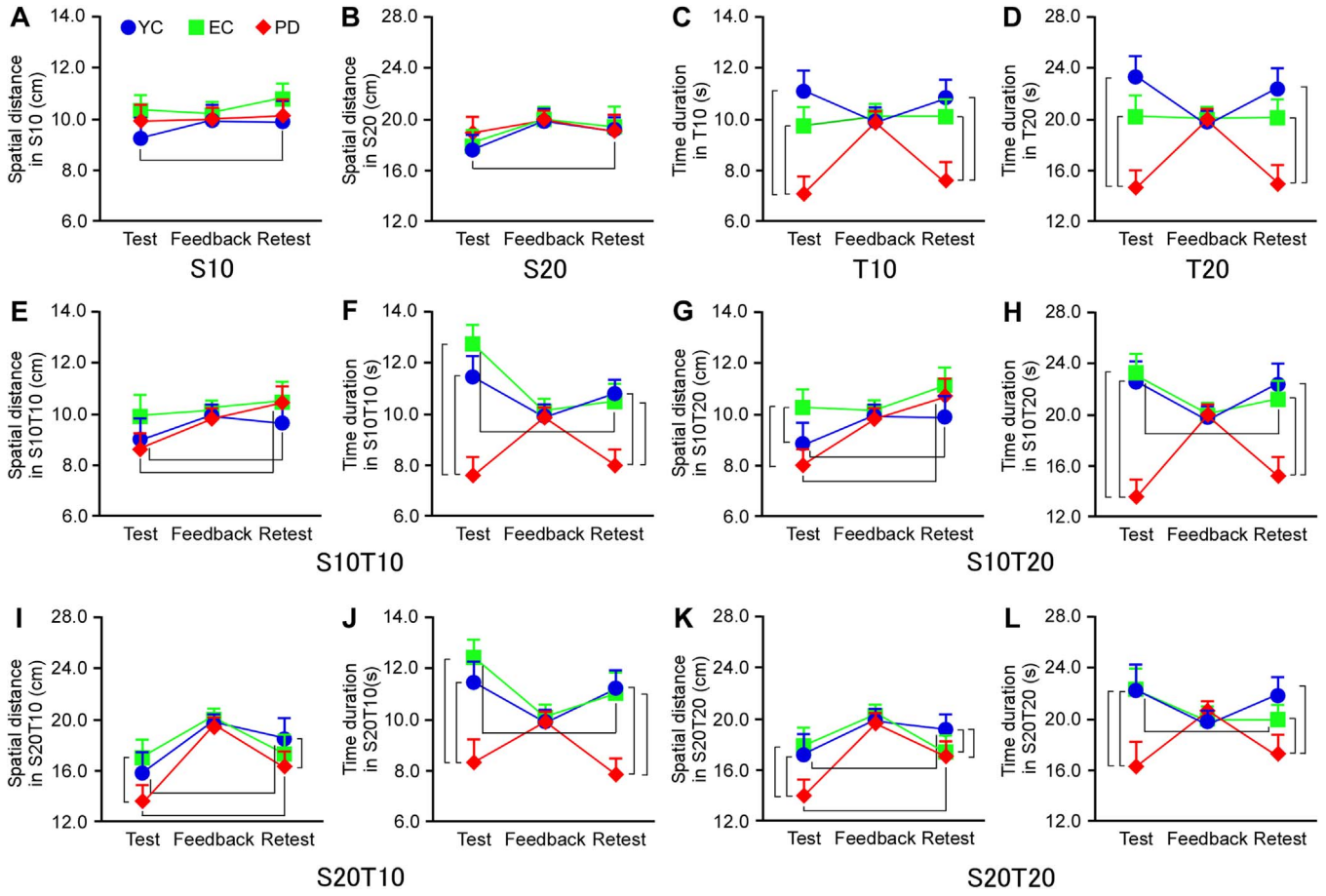


**Fig. 3.** Distance and duration production in test, feedback, and retest sessions. (A, B) Produced distance in the single production task. (C, D) Produced duration in the single production task. (E, G, I, and K) Produced distance in the concurrent production task. (F, H, J, and L) Produced duration in the concurrent production task. Connecting brackets indicate significant differences ($p < 0.05$). Error bars indicate SEM. YC = young control. EC = elderly control. PD = patients with Parkinson's disease.

condition, the *distances* under the "S20T10" ($t_{18} = 2.670$, adjusted $p < 0.05$) and "S20T20" ($t_{18} = 8.30$, adjusted $p < 0.001$) conditions were shorter. These results show that, in the test session, the patients underproduced the *distance* in the concurrent production task, relative to the single production task.

When similar analyses were also made in produced *duration*, it was found that, for the EC group, the produced *duration* in the concurrent production task was longer than in the single production task (Fig. 4C and D). In the "T10-related" combination analysis (Fig. 4C), the *durations* in the "S10T10" and "S20T10" conditions were longer than that in the "T10" condition only in the EC group. A two-way ANOVA revealed main effects of group and condition, as well as their interaction. Multiple comparisons showed that the *duration* for the PD group was shorter than those for the YC (adjusted $p < 0.05$) and EC (adjusted $p < 0.05$) groups. Post-hoc tests within the EC group showed that, compared with the "T10" condition, the *durations* under the "S10T10" ($t_{17} = 3.701$, adjusted $p < 0.05$) and "S20T10" ($t_{17} = 4.334$, adjusted $p < 0.05$) conditions were longer. The results of *duration* in the "T20-related" combination analysis were essentially the same as above (Fig. 4D): compared with the "T20" condition, the *durations* under the "S10T20" ($t_{16} = 3.032$, adjusted $p < 0.05$) and "S20T20" ($t_{17} = 8.238$, adjusted $p < 0.001$) conditions were longer. In contrast to the performances for the EC group, the produced *duration* for the PD group was stable across conditions in both the "T10-related" and "T20-related" combination analysis (Fig. 4C and D); that is, duration was stably underproduced.

Why did the PD group underproduce *distance* in the concurrent production task? Increases in random errors that are usually seen in the dual-task procedure (Yordanova et al., 2015; Corp et al., 2016) as opposed to single tasks cannot explain the results because the *duration* production in the patients reduced the accuracy of *distance* production during the concurrent task, not the precision; SEM did not significantly differ across conditions. Furthermore, the underproduction of *duration* cannot be explained by the dual-task procedure simply exacerbating already impaired performances in single tasks because there was no significant across-group difference in produced duration under the single-task conditions ("S10" and "S20"). If anything, the PD group yielded a statistically unsupported but slightly *longer* distance than the YC group in these single-production conditions; nevertheless, produced distance became markedly *shorter* for the PD group in the concurrent production.

### 3.2.4. *Effects of feedback*

Effects of feedback on later performance were examined by comparing performances between the test and retest sessions. In the single production task, the produced *distance* during retest was longer than that during test only for the YC group (Fig. 3A and B), whereas the produced *duration* did not differ (Fig. 3C and D). Post-hoc tests showed that, only for the YC group, the *distance* during retest was longer than that during test in the "S10" (post-hoc paired *t*-test, $t_{19} = 3.157$, adjusted $p < 0.05$) and "S20" ($t_{19} = 2.425$, adjusted $p < 0.05$) conditions. The same analyses were also performed for the "T10" and "T20" conditions, but none of the effects were significant.

The same analysis was also performed for the performances in the concurrent production task. Effects of feedback on the *distance* production were observed for the YC and PD groups (Fig. 3E, G, I, and K). Only for the YC and PD groups, post-hoc tests showed that the *distance* during retest was longer than that during test in the "S10T10" (PD: $t_{18}$

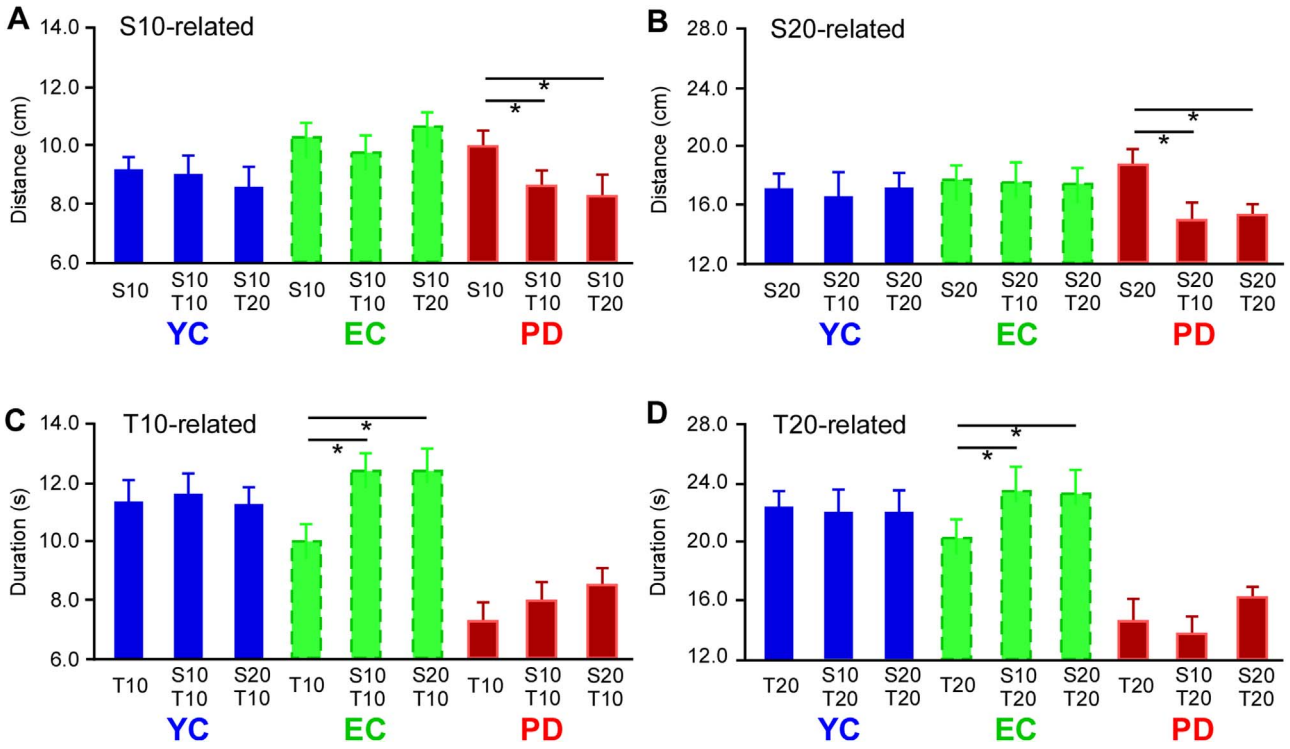


**Fig. 4.** Comparison between the single and concurrent productions. (A) Distance in the conditions belonging to the "S10-related" analysis. (B) Distance in the conditions belonging to the "S20-related" analysis. (C) Duration in the conditions belonging to the "T10-related" analysis. (D) Duration in the conditions belonging to the "T20-related" analysis. Asterisks indicate significant differences (*$p < 0.05$). Error bars indicate SEM. YC = young control. EC = elderly control. PD = patient with Parkinson's disease.

= 2.659, adjusted $p < 0.05$), "S10T20" (YC: $t_{19}$ = 3.480, adjusted $p < 0.05$; PD: $t_{18}$ = 5.353, adjusted $p < 0.05$), "S20T10" (YC: $t_{19}$ = 4.384, adjusted $p < 0.05$; PD: $t_{18}$ = 3.602, adjusted $p < 0.05$), and "S20T20" (YC: $t_{19}$ = 1.975, adjusted $p < 0.05$; PD: $t_{18}$ = 6.587, adjusted $p < 0.01$) conditions. In contrast, effects of feedback on the *duration* production were observed only for the EC group (Fig. 3F, H, J, and L). Only for the EC group, post-hoc tests showed that the *duration* during retest was shorter than that during test in the "S10T10" ($t_{17}$ = 2.861, adjusted $p < 0.05$), "S10T20" ($t_{17}$ = 2.861, adjusted $p < 0.05$), "S20T10" ($t_{17}$ = 2.633, adjusted $p < 0.05$), and "S20T20" ($t_{16}$ = 2.959, adjusted $p < 0.05$) conditions.

In the concurrent task, *duration* production in the EC group and *distance* production in the PD group were improved after the experience of the feedback session. For both groups, the dimension in which the performance was improved after the feedback session was consistent with the dimension in which the performance was reduced during the concurrent task in the initial test session.

### 3.3. Correlation between striatal DaT and production

The DaT imaging indicated that there was little accumulation of radiation in the striatum in the patients (Fig. 5A). The SBRs in the 19 patients negatively correlated with the UPDRS (Fig. 5B). For the single production task (Fig. 6A and B), the produced *durations* under the "T10" and "T20" conditions in the test session were strongly correlated with SBR. For the concurrent production task (Fig. 6C and D), the *durations* under the "S10T10" and "S20T20" conditions were correlated with SBR, but those under the "S10T20" and "S20T10" conditions were not (Table 2). Produced *distances* under all the conditions, on the other hand, lacked correlations with SBR. Note that participants were requested to move the pen at a constant speed of 1 cm/s in the "S10T10" and "S20T20" conditions, whereas the requested speeds in the "S10T20" and "S20T10" conditions were 0.5 cm/s and 2 cm/s, respectively.

These results indicate that striatal DaT deficit is related to *duration* production in both single and concurrent tasks, although this relationship may be speed dependent.

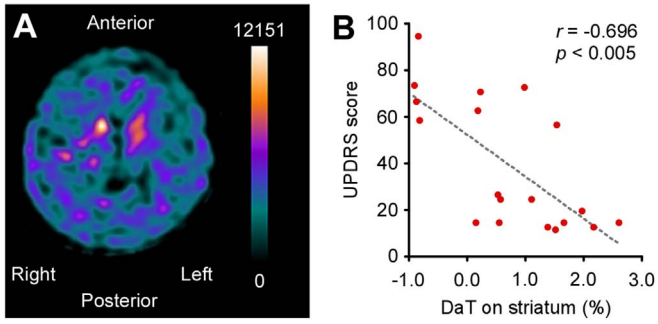


**Fig. 5.** Striatal DaT deficit in PD. (A) Binding radiation accumulation in a PD patient with Hoehn-Yahr stage 3 on striatal DaT imaging with coronal view. The numbers indicate binding radiation counts per pixel. The imaging show little accumulation of radiation in the striatum. (B) The specific binding ratio (SBR) in the striatum in PD was correlated to UPDRS. $r$ and $p$ indicate Pearson's correlation coefficent and the uncorrected $p$ value, respectively.

## 4. Discussion

In a manual action to move a pen for a specified distance and in a specified duration, we observed differences in performance between elderly and young participants as well as between PD patients and the young participants. Elderly participants exhibited impaired duration production when they had to produce distance and duration concurrently. On the other hand, no impairment was observed for single production of either distance or duration. In contrast, PD patients exhibited normal distance production and marked duration underproduction in single production task, but both distance and duration were underproduced in concurrent production task. Therefore, when participants were asked for concurrent production of space and time, they should have suffered from competition of limited cognitive

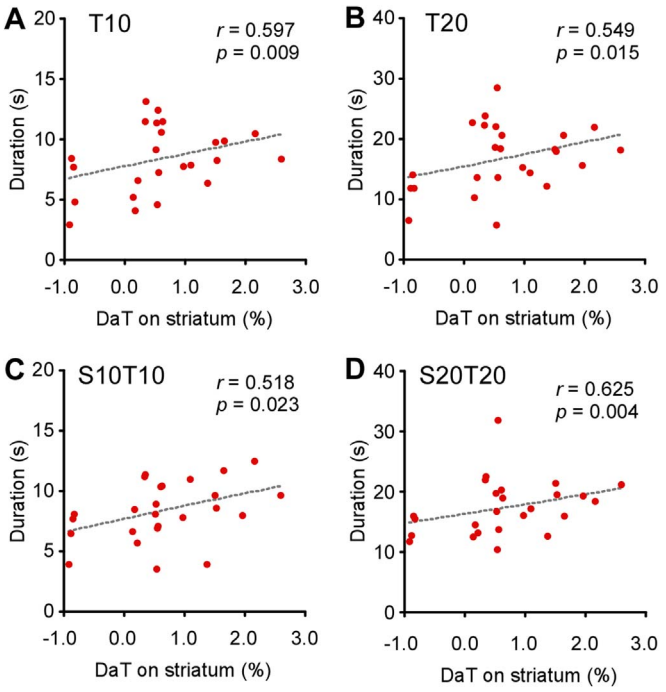


**Fig. 6.** Correlation between striatal DaT and produced duration. Each panel plots an across-patient scattergram between DaT as indexed by SBR in the striatum and produced duration in the behavioral conditions designated in each (A) "T10", (B) "T20", (C) "S10T10", and (D) "S20T20". The line indicates the best-fit linear regression. *r* and *p* indicate Pearson's correlation coefficent and the uncorrected *p* value, respectively.

**Table 2**
Correlation of DaT and distance/duration.

| Task | Condition (Test session) | Dimension | *r* | *p* |
|---|---|---|---|---|
| Single | S10 | Distance | 0.167 | 0.509 |
| | S20 | Distance | 0.425 | 0.069 |
| | T10 | Duration | 0.597 | 0.009 |
| | T20 | Duration | 0.549 | 0.015 |
| Concurrent | S10T10 | Distance | −0.114 | 0.643 |
| | | Duration | 0.518 | 0.023 |
| | S10T20 | Distance | 0.218 | 0.371 |
| | | Duration | 0.339 | 0.156 |
| | S20T10 | Distance | −0.040 | 0.870 |
| | | Duration | 0.341 | 0.153 |
| | S20T20 | Distance | 0.217 | 0.372 |
| | | Duration | 0.625 | 0.004 |

resources as seen in performances in dual tasks in general, but yielded performance changes as a systematic increase in constant error in one direction rather than random error. These findings suggest that normal aging yields impaired performances in both elderly participants and PD patients. Temporal underproduction in the PD patients appeared to "entrain" spatial production during spatiotemporal processing, as if the distance to be produced were made consistent with the abnormally shorter duration in perception and performance in these patients. We also observed that reduced striatal DaT was correlated with the extent of duration underproduction in PD patients.

Performance did not differ between PD patients and controls when spatial or temporal visual cue was presented, suggesting that all participants understood the task, were able to move the pen, and were able to pay attention to the cues, appropriately calibrating their motor actions in reference to the cue. According to cognitive assessment scores, both elderly participants and patients exhibited similarly compromised functioning as compared to young controls. This is consistent with previous studies showing normal aging to be associated with general decline of cognitive functioning (Axelrod et al., 1992; Freitas et al., 2011). However, none of our participants had any signs of dementia; their cognitive assessment scores were well within normal range.

Duration underproduction for PD patients in the single production task was similar to those reported in previous examinations of time production in PD patients (Pastor et al., 1992; Lange et al., 1995; Smith et al., 2007), altogether suggesting that they exhibit dysfunctional temporal processing (i.e., time compression). Furthermore, distance production in the single production task was normal for all participants, suggesting that purely spatial processing is unaffected by normal aging and PD.

Aging and PD affected spatiotemporal production performance differently. It may be because of aging per se if their performances similarly differ from those for young controls, but aging cannot explain why the patients and the age-equated elderly controls exhibited different patterns of results. Compared to the single production task, produced duration in the concurrent production task without cues was longer in the elderly group, although produced distance in this group was nearly identical between the concurrent and single production tasks, indicating that normal aging is associated with worse temporal processing in concurrent spatiotemporal production. In spatiotemporal comprehension, it is known that spatial representations have precedence over temporal ones in accuracy and precision (Boroditsky, 2000; Casasanto et al., 2010). In spatiotemporal production also, it is possible that elderly people spend a greater effort to accomplish accurate spatial production at the expense of some extra physical time exceeding a requested duration for production. In healthy elderly adults, spatial information may be used as a stable base on which further spatiotemporal processing can be based. In contrast, the patients produced shorter distances in the concurrent task than in the single distance task. However, duration remained stably underproduced in both the single duration task and the concurrent task, indicating disruption of spatial production only during the concurrent task, during which temporal underproduction in PD patients appeared to "entrain" spatial underproduction.

For the spatial underproduction during the concurrent task in PD patients, one might argue that group differences in single production could have been simply exacerbated with increasing task complexity, leading to a more pronounced deficit in the concurrent task. Our data showed that the deficit of duration production remained stable between the single and concurrent tasks, therefore the observed spatial underproduction in the concurrent task might have reflected an impact of increased task demands on impaired sensorimotor systems, such that a major fraction of cognitive resources is spent to prevent duration production from overt exacerbation at the expense of distance production. However, this scenario has a difficulty in explaining why distance production became consistently shortened, rather than extended or more prone to random error (Yordanova et al., 2015; Corp et al., 2016), in the concurrent task. If the spatial production error was simply caused by lesser allocation of cognitive resources to the spatial task in the condition of increased task demands, the error could be observed as spatial overproduction in some patients and underproduction in others, but the results unequivocally indicated distance underproduction in all patients. Therefore, we consider it more likely that the spatial underproduction occurred as an entrainment by temporal underproduction in PD patients. Nevertheless, in future studies we should recruit a larger number of patients to clarify to what extent the "entrained" distance underproduction in PD patients may correlate with their impaired duration production. Currently some conditions seemed to yield a slight tendency that those patients who exhibited more pronounced duration underproduction also produced a shorter distance in the dual task as compared with the single task (e.g., the "S10T10" condition, $r = 0.40$, $p = 0.094$), and our claim will be strengthened if such interobserver correlations are found to be the case.

With regard to cue feedback, in the single production task, an effect of feedback on distance production was observed in young participants. This suggests that young people have cognitive flexibility for distance

production. On the other hand, the absence of feedback effect in elderly and PD participants may indicate inadequacy of the feedback session for them, because they experienced only two trials per condition during the two blocks of the feedback session. Future research is required to examine how many trials are actually needed for these participants to exhibit a feedback effect, if any. In contrast, no participants yielded any feedback effect on duration production. This suggests that internal representation of duration may be stable within individuals. In the concurrent production task, effect of feedback on distance production was observed in young and PD participants, whereas effect of feedback on duration production was observed in elderly participants. The feedback effect on distance production in young participants may be similar to that for the single task. However, for PD patients, the improvement on distance production may be viewed as some alleviation of spatiotemporal entrainment after experience of the feedback session. On the other hand, the feedback effect on duration production in elderly participants may be viewed as some calibration to counteract erroneous duration production.

Mental time is thought to be processed by a complex neural network involving the frontal cortex, hippocampus, basal ganglia, and cerebellum (Hinton & Meck, 2004; Buhusi and Meck, 2005). Furthermore, the corpus striatum plays a central role in processing of time around a few tens of seconds (Honma et al., 2016). Correlation between DaT and produced duration in the single production task in the PD group suggests that disordered temporal processing is associated with striatal expression of DaT, which transports DA. On the other hand, the presence of correlation of DaT and produced duration at average speed (1 cm/s) of pen movement but the absence of correlation at faster (2 cm/s) and slower (0.5 cm/s) speeds in the concurrent production task suggests that this DaT-duration relationship is velocity sensitive. Moving the pen at a faster or slower speed may require greater attentional resources. For example, in the case of faster speed, transient attention may be required to achieve that speed as quickly as possible, whereas sustained attention may be required to maintain a steady state movement in the case of slower speed. In addition, no correlation between DaT and produced distance suggests that striatal dopaminergic neurotransmission does not play a marked role in spatial production. Although spatial processing occurs via connections from the visual cortex to the PC and then to the PFC (Quintana and Fuster, 1993; Chafee and Goldman-Rakic, 1998), the spatial production examined here may be unrelated to the PFC and striatum, for the patients with PD exhibited normal distance production in the single production task.

Our findings support the hypothesis that spatial and temporal processes interact during spatiotemporal processing, because one production was distorted so as to be more consistent with the other production during the concurrent task. PD patients, in particular, underproduced duration appeared to disrupt normal production of distance. Patients with PD may strictly adhere to temporal aspects, to which spatial aspects are entrained during spatiotemporal processing, possibly due to severe time compression associated with DA and/or DaT deficits. It is known that poverty of DA linked to deficient DaT protein in the striatum leads to hyper-activity or fast signal cycles in the globus pallidus and subthalamic nuclei (Delong, 1990; Bergman et al., 1994; Raz et al., 2000). Time compression may be associated with hyper-activity or fast signal cycles via a loop system such as striatum–pallidus–thalamus–cortex (Galvan et al., 2015). Furthermore, time compression may demand a high load for temporal processing, and the severe time compression may consolidate in patients with PD due to their prolonged symptom. Consequently, duration production may be given a higher priority than distance production during concurrent processing.

The current research revealed new aspects of spatiotemporal processing that are hardly noticed with healthy young adult participants alone. However, it remains to be seen whether young adults process space and time dimensions separately or interactively, since they accurately produce both distance and duration. It is possible that interactions between spatial and temporal processes occur at some early stage but are not made explicit as interactions in performance levels in young adults. It is also possible that each dimension is processed separately with sufficiently rich sensorimotor systems separately allocated to each processing (Pashler, 1994). Future research is required to reveal a possible mechanism for spatiotemporal production by increasing workloads, perhaps with extreme or variable speeds during task.

Our study has several limitations. First, the duration task was restricted to 10 s or 20 s. In the timing literature, it is known that PD patients overproduce a shorter duration (e.g., 8 s) and underproduce a longer duration (e.g., 21 s) (migration effect) (Malapani et al., 1998), and this effect occurs only when durations exceed 2 s (Koch et al., 2008). If we had reduced duration to a few seconds or within a subsecond range, different kinds of entrainment might have shown up. Second, PD patients were studied while medicated, because some patients suffered from too large tremor to manage the pen tablet under the *Off* condition, in which medicine was not being administered. As dopamine replacement promotes striatal functioning but can adversely affect frontal functions (Damier, 2015), comparative performance in the *Off* state is ideally required to determine the effects of medication. Finally, the absence of DaT scan data for normal controls was an inevitable limitation due to our own hospital's ethical guidelines. Nevertheless, our findings may help bridge the gap between striatal DaT/DA and spatiotemporal production.

Our approach may shed new light on the way temporal processing affects spatial processing, and vice versa, when they are concurrently active, and may be applicable to a wide variety of symptoms with distorted production, such as epilepsy (Drane et al., 1999), depression (Thönes and Oberfeld, 2015), schizophrenia (Su et al., 2015), and attention-deficit hyperactivity disorder (Suarez et al., 2013), among others. Furthermore, this easy-to-use approach using a tablet device may be useful in identifying previously undiagnosed disorders of spatiotemporal production and may reveal a mechanism underlying integration of space and time.

## Acknowledgements

This study was supported by Grant-in-aids for Scientific Research (KAKENHI) for Innovative Areas "The Science of Mental Time" [25119003 and 25119006], Scientific Research (C) [23591283], Exploratory Research [24650142], and Young Scientists [26860677]. This study was also supported in part by the Showa University Medical Foundation.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2017.06.004.

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