Published in final edited form as:

Brain Res. 2009 September 22; 1290: 12–20. doi:10.1016/j.brainres.2009.06.099.

The Effects of Parkinson's Disease and Age on Syncopated Finger Movements

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Abstract

In young healthy adults, syncopated finger movements (movements between consecutive beats) are characterized by a frequency-dependent change in phase at movement rates near 2 Hz. A similar frequency-dependent phase transition is observed during bimanual anti-phase (asymmetric) tasks in healthy young adults, but this transition frequency is significantly lowered in both patients with Parkinson's disease (PD) and older adults. To date, no study has examined the transition frequency associated with unimanual syncopated movements in patients with PD or older adults. This study examined the effects of movement frequency on the performance of unconstrained syncopated index finger flexion movements in patients with PD, older adult subjects matched to patients with PD, and young adult subjects. Syncopated movements were paced by an acoustic tone that increased in frequency from 1 to 3 Hz in 0.25 Hz increments. Movement phase was quantified and the movement frequency where subjects transitioned from syncopation to synchronization was compared between groups. The principal finding was a marked impairment in the ability of patients with PD to perform syncopated movements when off medication. Medication did not significantly improve performance. In addition, the transition frequency for older adult subjects was lower than young adult subjects. These findings demonstrate that, similar to bimanual tasks, the coordination dynamics associated with unimanual syncopated finger movements transition from a stable to an unstable pattern at significantly lower frequencies in patients with PD and older adults compared to young adults.

Keywords

syncopation; aging; Parkinson's disease; movement frequency

1. Introduction

To better understand the neural substrates of sensorimotor coordination, many studies have examined rhythmic coordination of a simple finger flexion movement with an auditory cue, such as synchronization (moving on the beat) and syncopation (moving between beats) (Jantzen et al., 2002; Jantzen et al., 2004; Jantzen et al., 2005; Jantzen et al., 2006; Jantzen et al., 2007; Kelso, 1992; Mayville et al., 2002; Mayville et al., 1999; Mayville et al., 2001). These

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studies have shown that the stability of these two movement timing states is frequency dependent. Young healthy subjects are able to successfully perform synchronized finger movements at tone frequencies above 3 Hz. In contrast, syncopated finger movements usually can only be performed up to frequencies near 2 Hz, at which point subjects spontaneously transition to a synchronization timing state (Kelso, 1992; Mayville et al., 2002; Mayville, 1999; Mayville, 2001). Based on this finding, it has been suggested that syncopation imposes a greater demand on neural networks mediating the temporal coordination of externally paced movements (Jantzen et al., 2002; Jantzen et al., 2004; Jantzen et al., 2005; Jantzen et al., 2007; Mayville et al., 2002; Mayville et al., 1999; Mayville et al., 2001). This idea is supported by imaging studies showing that, relative to synchronized movements, syncopation is associated with increased activity in cortical and subcortical areas that are implicated in movement timing processes, such as the supplementary motor area (SMA), basal ganglia, cerebellum, and lateral premotor areas (Jantzen et al., 2002; Jantzen et al., 2004; Jantzen et al., 2005; Jantzen et al., 2007; Mayville et al., 2002; Mayville et al., 1999). In particular, the supplementary motor area (SMA) is a region that is considered to play a crucial role in the timing of sequential or repetitive movements (Gerloff et al., 1997; Jenkins et al., 1994; Macar et al., 2004; Shima and Tanji, 1998; Tanji and Shima, 1994). Thus, populations who have impaired movement-related activity in the SMA, such as patients with Parkinson's disease (PD) (Haslinger et al., 2001; Jahanshahi et al., 1996; Limousin et al., 1997; Rascol et al., 1992; Sabatini et al., 2000; Samuel et al., 1997), would be expected to have significant deficits in the performance of a syncopation task.

A variety of studies have shown that patients with PD have impairments in timing during the performance of unimanual repetitive movements and that this impairment is frequency dependent. Simple repetitive finger movements are associated with an abnormal increase in timing variance at frequencies above 2 Hz (Nakamura et al., 1978; Pastor et al., 1992b). Moreover, there is a marked attenuation of movement amplitude and loss of phase when synchronized movements are performed at frequencies near to or above 2 Hz (Stegemöller et al., 2009). Patients with PD also have frequency-dependent deficits in bimanual movements. Studies of bimanual coordination have shown that movements transition from anti-phase (asymmetrical) to in-phase (symmetrical) at significantly lower frequencies in patients in PD compared to age-matched controls (Almeida et al., 2002; Byblow et al., 2002; van den Berg et al., 2000). Interestingly, the transition frequency from anti-phase to in-phase bimanual movements corresponds closely to the transition frequency associated with syncopated to synchronized movements in healthy young adults (Swinnen et al., 2004). These findings suggest that the transition frequency at which coordination dynamics transition from a stable to an unstable pattern is markedly lowered in patients with PD, irrespective of whether the movements are unimanual or bimanual. Older adults also have impairments in the control of movement timing during unimanual movements (Greene and Williams, 1993; Gunstad et al., 2006; Inui, 1997; Poston et al., 2008; Vanneste et al., 2001; Yan et al., 1998) and the coordination of bimanual movements (Stelmach et al., 1988; Wishart et al., 2000). This further suggests that the progressive degeneration of basal ganglia associated with aging (De Keyser, 1990; Pugh, 2002; Reeves et al., 2002) and PD may contribute to a lowering of the transition frequency associated with both uni- and bimanual coordination dynamics.

To date, no study has examined the performance of unimanual repetitive syncopated movements in patients with PD or older adults. The main purpose of this study was to examine if the frequency at which subjects transitioned from syncopated to synchronized movements was altered in either population relative to young healthy adults. An incremental frequency task was used whereby the tone frequency was increased from 1 to 3 Hz in 0.25 Hz increments (Kelso et al., 1992; Mayville et al., 2002; Mayville et al., 1999; Mayville et al., 2001) and the frequency at which subjects transitioned from syncopation to synchronization was quantified. We hypothesized that: (1) patients with PD would have a lower transition frequency than older

adults, (2) older adults would have a lower transition frequency than young adults, and 3) medication will increase the transition frequency in patients with PD.

2. Results

2.1 UPDRS Scores

Clinical evaluation of disease severity was assessed using the United Parkinson's Disease Rating Scale (UPDRS). There was a significant effect of medication on UPDRS total motor scores and finger taps ($t > 6.6$, $p < 0.001$) (Table 1).

2.2 Individual Results

Fig. 2 shows representative kinematic data from three subjects: one subject with PD, off and on medication, one older adult subject, and one young adult subject. Because each subject transitioned from syncopation to synchronization before 2.25 Hz, only data from 1 to 2.25 Hz is shown. The subject with PD in the off medication state was unable to perform syncopated movements at the lowest tone frequency tested. Antiparkinsonian medications improved the amplitude and frequency of movement, but the movements were neither synchronized nor syncopated with the tone. In contrast, both the young and adult subjects were able to syncopate movements above 1.5 Hz. The young adult subject maintained a steady phase near 180 degrees (optimal syncopation) up to 2 Hz while the older adult subject gradually transitioned from syncopation to synchronization during the 1.75 Hz condition.

2.3 Phase

Across all subjects with PD, there was a marked impairment in the performance of syncopated movements, even at low tone frequencies. This impairment was not significantly affected by medication. Five subjects with PD in the off medication state (PD_{OFF}) and 4 subjects in the on medication state (PD_{ON}) were unable to syncopate at 1 Hz respectively. Older adult subjects also consistently showed a deterioration of syncopation performance at lower frequencies than young adult subjects, but were capable of syncopating at 1 and 1.25 Hz. These differences across groups are demonstrated in the normalized phase histograms across subjects (Fig. 3A). The distribution of phase in young adult subjects was centered about ± 180 degrees (indicating syncopation) for tone frequencies of 1, 1.25, and 1.5 Hz, while for older adult subjects the distribution of phase was centered near ± 180 degrees for tone frequencies of 1 and 1.25 Hz. In contrast, the subjects with PD showed a phase distribution that remained relatively flat across all tone frequencies for both medication states, indicating a general impairment in syncopation.

The movement-to-movement variability in performance was assessed by calculating the standard deviation of movement phase with respect to a mean of 180 degrees (optimal syncopation) (Fig. 3B). Comparisons between the PD_{OFF} group and the young and older adult groups were conducted using a two-factor repeated-measures ANOVA (group $\times$ tone frequency). The results of this analysis showed main effects of group ($F(2) = 10.954$, $p < 0.001$) and frequency ($F(8) = 10.189$, $p < 0.001$) and an interaction effect of group $\times$ frequency ($F(2, 8) = 2.137$, $p = 0.008$). Planned contrasts between groups showed that the phase variation of the young adult group was significantly lower than both the older adults ($p = 0.023$) and the PD_{OFF} group ($p < 0.001$). The results of the post-hoc analyses of interaction effects are shown in Figure 3B (left plot). The phase variation in the young adult group was significantly lower than the PD_{OFF} group at 1.0, 1.25, and 1.5 Hz ($p < 0.004$), whereas differences between the older adult and PD_{OFF} group were only observed from 1.0 to 1.25 Hz ($p < 0.017$). The older adult group differed from the young adult group at 1.5 and 1.75 Hz ($p < 0.042$). Similar results were obtained for comparisons between the young and older adults and the same patients when on their medication (Figure 3B, center plot). This repeated measures ANOVA showed main effects of group ($F(2) = 10.791$, $p < 0.001$) and frequency ($F(8) = 9.783$, $p < 0.001$) and an

interaction effect ($F(2, 8) = 2.108, p = 0.009$). Planned contrasts showed that the phase variation of only the young adult group was significantly lower than the PD group ($p < 0.001$). Post-hoc analyses of interaction effects showed that the phase variation in the young adult group was significantly lower than the PD_{ON} group from 1.0 to 1.75 Hz ($p < 0.012$). Differences between the older adult and PD_{ON} group were only observed at 1.25 Hz ($p = 0.041$).

The effects of medication were analyzed using a two-factor ANOVA with repeated measures for medication (PD_{OFF} vs. PD_{ON}) and tone frequency. This analysis showed no main effect of medication ($F(1) = 0.280, p = 0.611$) or frequency ($F(1) = 0.953, p = 0.480$).

2.4 Transition Frequency

Fig. 4 shows the average transition frequency across subjects. Comparisons between the young adult, older adult and PD_{OFF} groups were conducted using a one-way ANOVA. This analysis showed significant main effects of group ($F(2) = 18.848, p < 0.001$). Planned contrasts revealed that the transition frequency was significantly lower in the PD_{OFF} group compared to both the young adult ($p < 0.001$) and older adult ($p = 0.009$) groups. The transition frequency of the older adult group was also significantly lower than the young adult group ($p = 0.027$). Similarly, main effects of group ($F(2) = 13.693, p < 0.001$) were obtained for comparisons between young adult, older adult and PD_{ON} groups. The transition frequency was significantly lower in the PD_{ON} group compared to the young adult group ($p < 0.001$). A paired samples t-test between subjects with PD off and on medication revealed was no significant difference in transition frequency between the medication states ($t = 0.195$).

3. Discussion

There are two main findings of this experiment. First, the patients with PD showed a marked impairment in the performance of syncopated finger movements, even at frequencies as low as 1 Hz, and this impairment was not significantly improved with antiparkinsonian medications. Second, the older adults also showed impairment in the performance of syncopated finger movements compared to young adults, but their performance was significantly better than the patients with PD. These findings are discussed with respect to previous studies showing that normal aging and PD are associated with deficits in movement timing and bimanual coordination and that these deficits are frequency-dependent.

In the present study, we found that the transition frequency associated with syncopated movements was significantly lowered in the patients with PD relative to both the older and younger adult groups. This finding is similar to studies that have examined the performance of bimanual coordination in PD (Almeida et al., 2002; Byblow et al., 2002; van den Berg et al., 2000). These studies have shown that patients with PD transition from anti-phase to in-phase movements at a significantly lower frequency than age-matched control subjects. However, the transition frequencies reported for bimanual movements were slightly higher (1.25 to 1.75 Hz) (Almeida et al., 2002; Byblow et al., 2002; van den Berg et al., 2000) than those observed in the present study (1.25 Hz or less). This discrepancy might be explained by the effects of medication in the patient sample tested (bimanual coordination studies were conducted only in the “on” medication state), or differences in the joint tested (finger flexion vs. elbow pronation/supination or wrist flexion/extension), suggesting a differential control of proximal and distal muscles. Alternatively, differences in the transition frequencies between bimanual and unimanual movements may reflect the differential role of ipsilateral and transcallosal pathways in the control of movement. Nonetheless, our findings and those from bimanual coordination studies suggest that subjects with PD have a generalized impairment in the neural substrates required to perform anti-phase movements (Almeida et al., 2002; Byblow et al., 2002; Geuze, 2001; Serrien et al., 2000; Swinnen et al., 2004; van den Berg et al., 2000; Verheul and Geuze, 2004), which may share similar neural substrates.

We also found that the transition frequency was significantly reduced in the older adult group relative to the young adult group. This finding suggests that normal aging is associated with changes in the function of the neural substrates that mediate the frequency-dependent transition from syncopation to synchronization. However, differences between groups may have been augmented by the fact that 6 of the 9 older adult subjects used their non-dominant hand to complete the task (matched to the PD group), while all young adult subjects used their dominant hand. Previous studies have shown that the performance of synchronized unimanual (e.g. Peters, 1980) and bimanual (e.g. Byblow et al., 1998; Peters, 1994; Treffner and Turvey, 1995, 1996; de Poel et al., 2007) movements is affected by hand dominance. However, it has yet to be shown if hand dominance affects the transition frequency associated with unimanual syncopated finger movements. Nonetheless, it is possible that the higher proportion of subjects that used their dominant hand in the young adult group may have contributed to the differences in the transition frequency between groups.

Movement timing impairments may have contributed to the reduction of the transition frequency associated with syncopated movements in both the older adult and PD groups. Studies examining movement timing in patients with PD have shown that the performance of low frequency (< 2 Hz) synchronized repetitive movements in patients with PD is comparable to that of age-matched controls (Harrington et al., 1998; Ivry and Keele, 1989; Ivry et al., 1988; Keele and Ivry, 1987; O'Boyle et al., 1996; Pastor et al., 1992). However, when synchronized movements are performed at frequencies near 2 Hz and above there is a marked increase in the variance of the inter-movement interval (Nakamura et al., 1978; O'Boyle et al., 1996; Pastor et al., 1992). This increase in movement timing variance has been attributed to a change in both motor output processes (motor-delay variance) and the function of a presumed internal time keeper (clock variance) (Harrington et al., 1998; Ivry and Keele, 1989; Ivry et al., 1988; Keele and Ivry, 1987; O'Boyle et al., 1996; Pastor et al., 1992). In contrast to people with PD, older adults have impairments in internal time keeping (Greene, 1993; Gunstad, 2006; Inui, 1997; Poston, 2008a; Vanneste, 2001; Yan, 1998), but not motor-delay variance (Greene, 1993; Inui, 1997; Yan, 1998). Thus, tasks that impose high demands on movement timing, such as syncopation, may lead to impaired movement performance in both older adults and patients with PD. However, this impairment may be exacerbated in patients with PD due to the additional impairment in motor delay.

The neural substrates mediating the control of syncopated movements are poorly understood. Studies in young healthy adults have shown that syncopated movements are associated with an increase in movement-related activity in the SMA, basal ganglia, cerebellum, and lateral premotor areas relative to synchronized movements (Jantzen et al., 2002; Jantzen et al., 2004; Jantzen et al., 2005; Jantzen et al., 2007; Mayville et al., 2002; Mayville et al., 1999). Transcranial magnetic stimulation studies have further shown that syncopation is associated with an increase in intracortical inhibition in the interval between movements (Byblow and Stinear, 2006). It was suggested that the increase in SMA activity during the performance of syncopated movements may represent an increase in activation of cortico-cortical connections that mediate intracortical inhibition of the primary motor cortex (Byblow and Stinear, 2006). Thus, movement-related cortical activity may be actively suppressed during the interval between movements to ensure precise temporal control of movement onset. In patients with PD, intracortical inhibition at rest (Bares et al., 2003; Buhmann et al., 2004; Lewis and Byblow, 2002; MacKinnon et al., 2005; Pierantozzi et al., 2001; Ridding et al., 1995; Strafella et al., 2000) and movement-related activity of the SMA (Albin et al., 1989; Haslinger et al., 2001; Jahanshahi et al., 1995; Limousin et al., 1997; Playford et al., 1992; Rascol et al., 1992; Sabatini et al., 2000; Samuel et al., 1997) are decreased. In contrast to patients with PD, movement-related activity in the SMA is increased in older adults relative to young adults (Gunstad et al., 2006; Hutchinson et al., 2002; Riecker et al., 2006; Sailer et al., 2000). It has been hypothesized that this increase in SMA activity may reflect a compensatory response associated with and an

age-related decline in basal ganglia-thalamocortical function (De Keyser et al., 1990; Pugh et al., 2002; Reeves et al., 2002). Thus, changes in the function of the SMA may contribute to impaired control of syncopated movements in both patients with PD and older adults (but see discussion of antiparkinsonian medications below). However, in the absence of physiological evidence of a direct link between impaired cortical or subcortical function and the observed behavioral deficits, the mechanisms mediating the disordered control of syncopated movements in patients with PD and older adults remains speculative.

If the SMA and associated basal ganglia-thalamocortical pathways play an important role in the control of syncopated movements (Jantzen et al., 2004), then it would be expected that antiparkinsonian medications (e.g. levodopa) that improve movement-related activity in the SMA in patients with PD (Dick et al., 1989; Haslinger et al., 2001; Jenkins et al., 1992) would also be associated with improvements in syncopated movements. However, we found that optimal medication did not significantly improve the performance of syncopated movements in our sample of patients with PD. Medication increased the transition frequency in only 2 of 9 subjects, and in those subjects the increase was merely by 0.25 Hz. The absence of improvement in syncopation performance contrasts with the significant effect of medication on clinical measures of hand function when assessed with the UPDRS. This discrepancy likely relates to the added movement timing constraint imposed by the syncopation instruction that is not examined in the repetitive hand movement tasks of the UPDRS. These results suggest that the performance of syncopated movements is mediated by pathways that are largely independent of the basal-ganglia thalamocortical pathways that are facilitated with exogenous dopamine replacement or agonist therapy.

The results of this study are the first to show that both older adults and patients with PD have impairments in the performance of repetitive syncopated movements. These impairments are frequency dependent suggesting that movement frequency may play a critical role in the manifestation of repetitive or sequential movement timing and performance impairments in older adults and patients with PD.

4. Methods

4.1 Subjects

Data were collected from 9 healthy young adult subjects (mean age = 27 ± 4 years, 6 male, 3 female), 9 older adult subjects (mean age = 66 ± 10 years, 4 male, 5 female), and 9 subjects with a diagnosis of idiopathic PD (mean age = 65 ± 11 years, 4 male, 5 female). The young and older adult subjects had no history of neurological illness or musculoskeletal disorder. Subjects with PD presented with an akinetic-rigid syndrome of the upper limb (score of 2 or greater on items 23-25 of the UPDRS) and had a history of good response to levodopa (defined as at least a 25% improvement in motor UPDRS) (Table 1). Older adult subjects were matched in age (± 3 years), gender, and handedness to subjects with PD. Young adults were matched in handedness (8 right handed, 1 left handed) to the patients with PD. Young and older adult subjects were tested once, while subjects with PD were tested after an overnight 12-hour period of withdrawal from medication and again 1 hour after taking their normal dose of their optimal medication regimen (Table 1). The motor section of the UPDRS was conducted prior to performing the movement task in both medication states. All subjects gave written informed consent and the Institutional Review Board of Northwestern University approved the procedures.

4.2 Movement Task

All subjects were asked to complete syncopated movements of the index finger using a movement task comparable to the paradigm described by Kelso and colleagues (Kelso et al.,

1992; Mayville et al., 2002; Mayville et al., 1999; Mayville et al., 2001). A series of acoustic tones (50 ms, 500 Hz, 80 dB) were presented from a rate of 1.0 Hz to 3.0 Hz in increments of 0.25 Hz. For each increment, the rate was maintained for 15 intervals, for a total of 135 possible movements (Fig. 1). Subjects sat in a chair with their shoulder abducted to 30 degrees, elbow flexed at 90 degrees, and forearm in a semi-pronated position with the palm facing downward. The forearm, palmar aspect of the hand, thumb and fingers 3 to 5 were supported restricting movement to the index finger. Subjects were asked to complete each index finger flexion “in between tones” (syncopate) (Fig. 1) starting from a neutral position and flexing to approximately 25 degrees. Subjects were asked to maintain a 1:1 stimulus/response ratio and to not intervene if they began to transition to moving “on the tone” (synchronize). Subjects were also asked not to use any additional strategies, such as moving another body part on the beat, mentally doubling the beat, or extending the index finger on the beat to accomplish syncopation. No external feedback was provided, and subjects were free to adjust movement amplitude in order to maintain a 1:1 stimulus/response ratio. Eight of 9 patients with PD used their most affected hand to complete the task, resulting in 6 patients who used their non-dominant hand to complete the task. Because older adult subjects used the same hand as their matched counterpart, there were also 6 older adult subjects who used their non-dominant hand. All young adult subjects used their dominant hand to complete the task. Before data collection, subjects were given a minimum of 3-4 practice trials to ensure understanding of the task requirements. Young and older adult subjects completed 5 trials, while subjects with PD completed 5 trials in both the off and on medication states. Two minutes of rest was provided in between trials to prevent fatigue.

4.3 Data Collection and Analysis

Finger movement was captured using a uni-axial accelerometer (Entran EGCS-DIS-25) placed on the dorsum of the middle phalanx of the index finger. Data was collected at 2000 Hz using a data acquisition board (Power 1401, Cambridge Electronic Design, UK) and software (Signal 2, CED). The acceleration signal was processed by applying a 60 Hz notch filter to remove any mains noise and implementing a 4th-order Butterworth high-pass filter with a 1 Hz cut-off to eliminate any DC bias resulting in zero mean signals. Finger displacement was derived by double integrating the acceleration signal using a modified trapezoidal rule algorithm.

Movement phase relative to the tone was calculated from the time interval between the peak flexion displacement and the nearest tone. The distribution of phase was represented using a phase histogram and cumulative sum function averaged across subjects and completed for each tone frequency (1 – 3 Hz). For the phase histogram, the total number of movements in each 10-degree bin was counted from –180 to 180 degrees. The cumulative sum function was obtained by successively summing the total number of movements in each 10-degree bin from –180 to 180 degrees. Due to the variability in total number of movements performed across subjects, both the phase histogram and cumulative sum function were normalized to the maximum number of movements at each tone frequency. To obtain a measure of phase variation (distribution of phase across bins), the standard deviation was calculated with respect to a mean phase of 180 degrees (optimal syncopation) and averaged across subjects for each tone frequency (1 – 3 Hz). The cumulative sum function was used to obtain the transition frequency. For each tone frequency, the phase at which the total number of movements exceeded 50% was determined and labeled as the mean phase. The tone frequency in which there was a phase shift of greater than 90 degrees from the phase at the tone frequency of 1.0 Hz was determined as the transition frequency (i.e. the frequency in which subjects were no longer performing syncopated movements). In the cases where a subject was not able to syncopate at the lowest tone frequency tested, the transition frequency was denoted as 1.0 Hz. The transition frequency was determined across all five trials for each subject and then averaged over groups.

Phase variation was analyzed using a two-factor analysis of variance (ANOVA) with repeated measures where the within-subjects factor was movement frequency and the between-subjects factor was group. Separate ANOVAs were conducted for the comparisons of PD_{OFF} vs. older adults vs. young adults, PD_{ON} vs. older adults vs. young adults, and PD_{OFF} vs. PD_{ON}. Planned contrasts were conducted to examine group differences for the ANOVAs with comparisons across three groups. Post-hoc analysis of interaction effects were tested using Tukey's Honest Significant Difference (HSD) test. For the transition frequency variable, a oneway ANOVA was conducted with planned contrasts between groups. Separate ANOVAs were conducted for the comparisons of PD_{OFF} vs. older adults vs. young adults and PD_{ON} vs. older adults vs. young adults. Comparisons between the off and on medication states in the subjects with PD for the transition frequency and UPDRS variables were analyzed using paired t-tests.

Acknowledgments

This project was supported by NIH Grant R01 NS054199 and a grant from the Parkinson Alliance. We thank Mr. Fang Gao and Dr. Lance Myers for their assistance with the data. We thank the volunteers that participated in this study.

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Fig. 1.
(A) An example of syncopated movement performance and **(B)** timing of the tones for the IFT paradigm.

Fig. 2.
Raw position data is shown from one subject in each group. Boxes indicate time segments with syncopated movements.

Fig. 3. (A) Mean and standard error for normalized phase histograms. (B) Mean and standard error for phase variation. Interaction effects are shown. * = significant difference between the PD and the young adult group, $p < 0.05$. $\dagger$ = significant difference between the PD and the older adult group, $p < 0.05$. # = significant difference between the young adult and the older adult groups, $p < 0.05$.

Fig. 4. Mean and standard error for transition frequency. Asterisks designated differences between groups. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 1

Patient medications and UPDRS scores.

Patient	Medications (Dose in mg)	UPDRS Item 23 Hand Tested Off / On	UPDRS Item 23 Both Hands Off / On	UPDRS Items 23-25 Hand Tested Off / On	UPDRS Total Motor Score Off / On
1	C/L ((75/100), E (600), A (200), P(4.5)	2.5 / 1.5	2.5 / 1.5	6.5 / 3.5	22 / 7.5
2	C/L (100/400), E (800), A (200), P (6)	2.5 / 1	3.5 / 1	6.5 / 3	20.5 / 8
3	C/L (125/500), E (800), P (3.75)	2 / 1	5 / 2	5 / 2	37 / 20
4	C/L (137.5/550), CCR (50), E (1000), LCR (200), P (4)	3.5 / 2	6.5 / 4	9.5 / 5	51 / 24.5
5	C/L (125/500), R (12), CCR (250), LCR (1000)	3 / 2.5	6 / 4.5	5 / 3	34 / 19
6	C/L (50/200)	2 / 1	4 / 2	4 / 2	25.5 / 11
7	C/L (100/400)	1 / 0.5	2 / 0.5	4 / 2	21 / 15
8	C/L (50/200)	2 / 1.5	4 / 3	6 / 5.5	27.5 / 19
9	C/L (162.5/650)	1 / 1	2 / 1.5	3 / 3	26.5 / 19
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Mean $\pm$ 1 Standard Deviation		2.2 $\pm$ 0.83 / 1.3 $\pm$ 0.61	3.9 $\pm$ 1.65 / 2.2 $\pm$ 1.35	5.5 $\pm$ 1.92 / 3.2 $\pm$ 1.28	29.4 $\pm$ 9.85 / 15.8 $\pm$ 5.89
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Statistics		t = 5.000, p = 0.001	t = 6.200, p < 0.001	t = 4.824, p < 0.001	t = 6.600, p < 0.001

UPDRS = United Parkinson's Disease Rating Score, Item 23 = repetitive index finger-to-thumb tapping, Item 24 = repetitive hand opening/closing, Item 25 = repetitive forearm pronation/supination. C/ L = carbidopa/levodopa, CCR = carbidopa controlled release, LCR = levodopa controlled release, E = entacapone, A = amantadine, P = pramipexole, R = ropinirole.