Hand rhythmic tapping and timing in Parkinson’s disease

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Abstract

Background. Dysrhythmia is one of the features frequently associated with the motor disturbance in Parkinson’s disease (PD). The mechanism responsible for this phenomenon is not known.

Objectives. To assess the rhythmic movements of the hand in PD patients in general and in parkinsonian subtypes.

Methods. Fifty-one PD patients (32 males) with mean age 66.3 ± 9.1 years (6.6 years of symptoms) and 36 healthy controls (age 64.9 ± 13.2, range 40–85) were studied. Subjects were asked to tap with their dominant or less affected arm on a digitized switch board at their most comfortable pace (16 s), fastest tapping speed (12 s), and at different frequencies provided by a metronome. The mean rhythm and the tap-to-tap variation were compared. Performance of the PD patients and control subjects were compared, as there were different subtypes of PD patients. Patients were subclassified into: tremor predominant (TP) (14 patients), freezing predominant (FP) (11 patients), akinetic-rigid (AR) (12 patients) and an unclassified group (UC) (14 patients).

Results. There was no significance difference between patients and controls in the self-chosen, most comfortable tapping rate or in the tap-to-tap variation of the self-paced task. PD patients tapped at a significantly slower rate than controls when asked to tap at their fastest rate (4.39 ± 1.32 vs. 5.14 ± 1.31 Hz; \(p = 0.01\)). This difference was the result of an especially slow performance of the TP and AR subgroups (3.85 ± 1.20 and 3.88 ± 1.46, respectively; \(p < 0.01\), compared to the control group).

TP was the only subgroup to show an increased tap-to-tap variation at their fastest tapping rate compared to the control group (0.070 ± 0.057 vs. 0.029 ± 0.025 s, respectively, \(p < 0.05\)).

The TP subgroup also showed hastening when they followed an externally given rhythm of 2.5 Hz and they tapped at 2.73 ± 0.36 Hz (\(p < 0.05\)).

Conclusions. Externally driven and self-paced tapping are preserved in patients with PD, when examined at their best ‘on’ state. The tremor predominant subgroup seems to have specific pacing disturbances.

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1. Introduction

Bradykinesia, a common and poorly understood sign in Parkinson’s disease (PD), might be associated with disturbances in the execution of normal motor rhythm [1]. In people suffering from PD, a putative ‘internal clock’ is disturbed. Affected people tend to display slow movement activity and bradykinesia. They also lose their ability to make movements at a constant rhythm, resulting in dysrhythmicity.

This disturbed ‘internal clock’ that is presumably associated with difficulties in maintaining rhythmic movements, is a possible basis of freezing of gait (FOG) [2–4] festinating gait [5], motor blocks during performance of a manual tapping task [6], or difficulties in keeping a specific external rhythm while performing finger tapping [1]. Such abnormal timekeeping can be the result of disturbed time perception or motor timing, processes that are frequently engaged during timekeeping operations [7].

The underlying pathology in PD that leads to the timing disturbances described above is complicated and not fully understood. However, abnormal output from the basal ganglia to thalamus and cortex clearly contribute to dysrhythmicity that can be corrected by pallidotomy or deep brain stimulation [8–11].
Indirect effects of the primary dopaminergic deficit of PD on basal ganglionic circuits ultimately influence cortical activity, and, in particular, the supplementary motor area (SMA) [12]. The role of the SMA in rhythm reproduction has been the focus of a few recent studies. Halsband [13] showed by means of paced finger tapping tests that patients with SMA lesions were impaired in the reproduction of rhythms in the absence of an auditory cue. However, Harrington [14] suggested that internal timing processes in both time perception and motor-timing operations were mediated by the basal ganglia.

Patients with PD often can improve their motor performance (e.g. gait, speech) when they are asked to follow a given rhythm (external cueing) compared to following their internal self-initiated pacing (internal cueing) [15–17]. In addition, PD patients tend to start a repetitive movement well but after a short period of time the rhythm breaks down and becomes dysrhythmic [18]. PD patients tend also to tap too rapidly when instructed to tap at lower (1–3 Hz) frequencies and too slowly when instructed to tap at higher frequencies (5 Hz). In addition, the variability of their tapping rhythms is generally greater than that observed in controls [15].

A paradoxical observation is that some patients with PD have difficulty maintaining certain rhythms and tap at higher rates than asked for. For example, when instructed to tap at a frequency of a 3 Hz tone, they tap at 4 Hz. This phenomenon, called ‘hastening’, was first described by Nakamura [1]. Nagasaki [19] showed that this phenomenon exists also in elderly healthy subjects, suggesting that hastening may not be specific to PD.

Our general objective was to investigate disturbances in rhythm formation in PD. To that end, we studied the rate and regularity of self-generated rhythms under different circumstances. In addition, we studied whether hastening exists in PD to a greater degree than in healthy elderly subjects. We examined further whether certain subtypes of PD display different rhythmic behaviors.

### 2. Methods

#### 2.1. Subjects

Fifty-one PD patients (32 males) and 36 healthy control subjects (17 males) were tested (Table 1).

The diagnosis of PD was made by a movement disorders specialist, based on the United Kingdom Brain Bank clinical criteria [20]. PD subjects were tested in their best state (while at ‘on’ state) after the administration of their regular medications.

All patients underwent routine neurological examinations. Exclusion criteria included: dementia according to DSM IV criteria, concurrent neurological illness, pyramidal signs, or significant autonomic failure if it had appeared early in the course of the disease. Hand dominance was determined as the hand with which the subject had written since childhood. The Helsinki Committee of Tel Aviv Sourasky Medical Center approved the study, and all patients provided informed consent.

In addition to looking at the entire PD population, we also classified the PD patients into four subtypes, as first suggested by Jankovic [21]. The subtypes were as follows: tremor predominant (TP), freezing predominant (FP), akinetic-rigid (AR), and unclassified (UC). Briefly, patients with TP had tremor as the most significant and leading symptom with mild bradykinesia, rigidity or freezing. FP patients had experienced FOG as the most disturbing symptom. FOG was defined as transient episodes, lasting seconds, in which gait is halted and the patient reports experiencing the feeling that the feet are glued to the ground [2,22]. We considered subjects as FP if they scored 2 or higher on the freezing question #14 in the UPDRS part II at ‘off’ state. AR refers to subjects who had significant slowness in their movements (bradykinesia) and an increased muscle-tone (rigidity) but minimal, if any, tremor at rest.

The UC group refers to patients in which none of those features is significantly dominated over the others. The subclassification of patients was done prior to the testing by NG. The testing supervisor (GY) and statistician were blinded to the clinical diagnosis. Our control subjects were recruited randomly and consisted mainly of hospital workers and caregivers of the patients. None of the control subjects was taking anti-parkinsonian medications, benzodiazepine, or any other medication that might affect their performance. All control subjects were self-declared healthy persons.

### 3. Experiment

Our experimental method was adapted from Nagasaki [23]. The subject was seated in a reclining chair with the arm resting on the armrest. The tapping was performed with the less affected hand (PD patients) or dominant hand (control subjects). The subject placed the hand on a board

<table>
<thead>
<tr>
<th>Table 1 Characteristics of the study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Controls</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>AR</td>
</tr>
<tr>
<td>UC</td>
</tr>
<tr>
<td>FP</td>
</tr>
<tr>
<td>TP</td>
</tr>
</tbody>
</table>

PD refers to the entire patients with Parkinson’s disease; AR, akinetic-rigid type; UC, unclassified; FP, freezing predominant; TP refers tremor predominant; m, male; f, female; and SD, standard deviation.
Subjects were asked to tap at their most comfortable pace for 16 s. The purpose of this task was to see whether there were systematic preferred frequencies within the subgroups. We also evaluated mean frequency and tap-to-tap variation differences between the PD group and controls in the self-chosen tapping frequency.

3.2. Paradigm 2

Subjects were asked to tap for 12 s at their fastest pace. Here, too, we determined systematic differences in frequency and variance of the tapping among the study subgroups and in comparison to controls.

3.3. Paradigm 3

Subjects were instructed to tap at a rhythm given by a metronome at frequencies of 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 Hz, each lasting 10 s with breaks of 5 s in between. The essence of this exercise was to see how well subjects could follow the cueing at a wide range of frequencies. This paradigm was designed to probe for the hastening phenomenon.

3.4. Paradigm 4

Similar to paradigm 3, subjects tapped at the frequency of a metronome, but there were two alternating frequencies of 1 Hz lasting 15 s and 2.5 Hz lasting 10 s. This was done in order to determine how PD patients adjust themselves to abrupt changes in rhythm. We expected that hastening could also be exhibited in this paradigm.

In all four paradigms, we calculated the mean and variation in the time of tap onset, i.e. the standard deviation (SD) of the inter-response-interval within each trial, averaged across all subjects. We also calculated the coefficient of variance (CV) in tapping, i.e. variability normalized to mean value (CV = 100 × SD/mean).

We correlated tapping performance with duration of disease, type of disease, aging, and stage of the disease.

3.5. Statistics

ANOVA was applied to test for differences in tapping frequencies, tapping variations, and CV in tapping between the PD subgroups and the control group.

Contrast tests were used to compare each subgroup to the control group as well as for pairwise comparisons among the PD subgroups. Subjects who failed to complete all four paradigms were excluded from the study. Outliers were determined using box plots and were eliminated from further analysis.

Repeated measures ANOVA was applied to compare groups when the mean of tapping and its SD were measured in different frequencies. Likewise, the mean and SD of the variation between tap-to-tap were measured.

Hastening was defined in a group if that group showed a statistically significant faster tapping frequency than that of the control group. A criterion of $p < 0.05$ was used in all tests for statistical significance. Statistical analyses were performed using SAS software release 8.2 (Cary, NC, USA).

4. Results

4.1. Paradigm 1: self-initiated most comfortable tapping pace

When subjects were requested to tap at a pace that was most comfortable for them, average-tapping rates ranged from 0.56 to 4.47 Hz for the entire study population. No significant difference was found between the control and PD groups ($1.72 ± 0.91$ vs. $1.46 ± 0.53$ Hz: $p > 0.05$). When we divided the PD group into subgroups and compared each subgroup to the control group, no significant difference was observed as well. However, as shown in Table 2, when comparing the PD subgroups, we found a significant difference between the UC and FP groups ($p < 0.05$). There was no difference in the tapping variation between the PD patients and controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>$N$</th>
<th>Self-chosen* (Hz)</th>
<th>Fastest self-paced (Hz)</th>
<th>Tap-to-tap variation (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>36</td>
<td>$1.72 ± 0.91$</td>
<td>$5.14 ± 1.31$</td>
<td>$0.029 ± 0.025$</td>
</tr>
<tr>
<td>PD group</td>
<td>51</td>
<td>$1.46 ± 0.53$</td>
<td>$4.39 ± 1.32**$</td>
<td>$0.051 ± 0.046$</td>
</tr>
<tr>
<td>AR</td>
<td>12</td>
<td>$1.40 ± 0.61$</td>
<td>$3.88 ± 1.46**$</td>
<td>$0.049 ± 0.047$</td>
</tr>
<tr>
<td>UC</td>
<td>14</td>
<td>$1.29 ± 0.44$</td>
<td>$4.97 ± 1.27**$</td>
<td>$0.041 ± 0.039$</td>
</tr>
<tr>
<td>FP</td>
<td>11</td>
<td>$2.04 ± 1.00$</td>
<td>$4.90 ± 0.96$</td>
<td>$0.043 ± 0.042$</td>
</tr>
<tr>
<td>TP</td>
<td>14</td>
<td>$1.52 ± 0.30$</td>
<td>$3.85 ± 1.20**$</td>
<td>$0.070 ± 0.057**$</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01; in comparison to the control group.

* The most comfortable pace chosen by the person to tap for 16 s.
Table 3
Tapping frequencies (mean ± SD) in two externally driven alternating frequencies without an intervening rest period

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>1 Hz</th>
<th>2.5 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>36</td>
<td>1.06 ± 0.08</td>
<td>2.53 ± 0.23</td>
</tr>
<tr>
<td>PD group</td>
<td>51</td>
<td>1.04 ± 0.04</td>
<td>2.60 ± 0.28</td>
</tr>
<tr>
<td>AR</td>
<td>12</td>
<td>1.06 ± 0.08</td>
<td>2.67 ± 0.33</td>
</tr>
<tr>
<td>UC</td>
<td>14</td>
<td>1.03 ± 0.03</td>
<td>2.45 ± 0.30</td>
</tr>
<tr>
<td>FP</td>
<td>11</td>
<td>1.05 ± 0.05</td>
<td>2.54 ± 0.09</td>
</tr>
<tr>
<td>TP</td>
<td>14</td>
<td>1.04 ± 0.02</td>
<td>2.73 ± 0.36*</td>
</tr>
</tbody>
</table>

*p < 0.05, in comparison to the control group.

4.2. Paradigm 2: self-initiated fastest tapping pace

In contrast to the results of paradigm 1, PD subjects as a group tapped at a significantly slower rate than controls (4.39 ± 1.32 vs. 5.14 ± 1.31 Hz; p < 0.01). Further examination of the PD subjects within the subgroups identified that the TP and AR subgroups were slower than the control group (p < 0.01, Table 2). There was no difference between the PD group and control group in the variation within the tapping for this task. However, there was a significant difference in the variation of tapping between TP and the controls (p < 0.05, Table 2).

4.3. Paradigm 3 and 4: multiple frequencies and frequency switching protocols

No age effect was found in the control group at any frequency in paradigm 3, or in paradigm 4. Therefore, we referred the control group as a whole for subsequent analysis.

In paradigm 3 in which the external pacing frequency (2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0 Hz) was increased stepwise with a 5 s rest in between steps, there was no difference in the mean frequency between the entire PD group and the control group. There was no significant difference in the variation of tapping within the PD subgroups.

Analysis of average-tapping frequencies identified a trend to hastening in the FP subgroup at 2.5 Hz when they tapped at 3.02 ± 0.77 Hz, however, it was only marginally significant (p = 0.09).

Table 4
Variation of tapping frequencies (mean ± SD) in stepwise increased frequencies with rest intervals

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>4 Hz</th>
<th>4.5 Hz</th>
<th>5 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>36</td>
<td>0.033 ± 0.021</td>
<td>0.033 ± 0.029</td>
<td>0.027 ± 0.021</td>
</tr>
<tr>
<td>PD</td>
<td>51</td>
<td>0.050 ± 0.049</td>
<td>0.044 ± 0.040</td>
<td>0.037 ± 0.038</td>
</tr>
<tr>
<td>AR</td>
<td>12</td>
<td>0.058 ± 0.057*</td>
<td>0.056 ± 0.044</td>
<td>0.037 ± 0.027</td>
</tr>
<tr>
<td>UC</td>
<td>14</td>
<td>0.036 ± 0.031</td>
<td>0.023 ± 0.018</td>
<td>0.031 ± 0.026</td>
</tr>
<tr>
<td>FP</td>
<td>11</td>
<td>0.041 ± 0.038</td>
<td>0.037 ± 0.026</td>
<td>0.021 ± 0.010</td>
</tr>
<tr>
<td>TP</td>
<td>14</td>
<td>0.064 ± 0.061**</td>
<td>0.060 ± 0.053*</td>
<td>0.055 ± 0.059*</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01, in comparison to the control group.

Table 5
Variation of tapping timing in paradigms 2 and 4, expressed by the coefficient of variance (CV) of tapping in PD subgroups and the control group

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>At fastest tapping</th>
<th>At 1 Hz externally cued</th>
<th>CV 2.5 Hz externally cued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>36</td>
<td>13.21 ± 9.68</td>
<td>10.39 ± 1.67</td>
<td>12.22 ± 5.49</td>
</tr>
<tr>
<td>PD group</td>
<td>51</td>
<td>19.63 ± 16.52*</td>
<td>10.17 ± 1.96</td>
<td>9.53 ± 4.28*</td>
</tr>
<tr>
<td>AR</td>
<td>12</td>
<td>16.12 ± 15.89</td>
<td>9.73 ± 2.20</td>
<td>10.07 ± 4.30</td>
</tr>
<tr>
<td>UC</td>
<td>14</td>
<td>18.41 ± 16.47</td>
<td>9.79 ± 2.38</td>
<td>8.40 ± 2.68*</td>
</tr>
<tr>
<td>FP</td>
<td>11</td>
<td>20.31 ± 19.79*</td>
<td>10.49 ± 1.26</td>
<td>9.11 ± 4.31</td>
</tr>
<tr>
<td>TP</td>
<td>14</td>
<td>23.32 ± 15.33*</td>
<td>10.68 ± 1.78</td>
<td>10.58 ± 5.55</td>
</tr>
</tbody>
</table>

CV is variability, normalized to mean value (CV = 100 × SD/mean). *p < 0.05, comparing to the controls.

In paradigm 4, when patients switched between 1 and 2.5 Hz without an intervening rest period, there was no significant difference in mean frequencies between the PD group and control group. However, among the different PD subgroups, the TP subgroup tapped at a significantly higher rate than the controls (p < 0.05, Table 3). There was no difference in variation of tapping in both paradigms between the PD group and control group. However, we found in paradigm 3 significant differences in tapping variation within the PD subgroups. The TP subgroup showed a greater variation in tapping when they followed the cueing at frequencies of 4, 4.5, and 5 Hz (Table 4). The AR subgroup showed also a greater variation at frequency of 4 Hz. We did not find significant differences in frequencies lower than 4 Hz.

In paradigm 4, we did not find differences in the variation of tapping within the subgroups.

Older age was not a risk factor for hastening among the control group.

The PD group showed a significant higher CV in tapping, in the fastest tapping task, comparing to the control group, and significant lower CV at 2.5 Hz, when subjects followed two alternating frequencies (1 and 2.5 Hz), following an external cue (p < 0.05, Table 5). Looking into the subgroups, FP and TP tapped with a significant higher CV, compared to the control group (p < 0.05, Table 5). The UC subgroup showed a significantly lower CV when they switched from 1 to 2.5 Hz, following an external cue (p < 0.05, Table 5).

5. Discussion

The results of this study yielded two major findings. First, by subdividing the PD group into four subgroups, we could specify some known parkinsonian rhythm disorders that were previously attributed to the entire PD group, and now might be attributed to one or more specific subgroups. Second, we introduced another means of evaluation by using the variation of tapping.
PD patients showed a significantly higher CV when they used their own internal clock (paradigm 2), as opposed to their lower CV following an external cue (paradigm 4), compared to the control group. This observation suggests that the external cue compensates the disturbed internal clocking in PD patients and improves their performance. In contrast, it interferes with the functional internal clocking of the control subjects, and therefore, their performance is seemingly compromised.

The TP subgroup showed the most consistent evidence of rhythm disturbances, in both the internally as well as the externally driven trials. Mean tapping and tapping variation differed in the TP subgroup.

The hastening phenomenon, observed in the TP subgroup, was triggered by switching between two externally driven frequencies. We propose that hastening is related to tremor in an unknown way. The fact that only the TP subgroup of patients developed the hastening phenomenon was also observed by Freund [24] who suggested that patients use the tremor generator to compensate for their difficulty in producing serial hand movements faster than 2 Hz.

In contrast to others [1,15,25], we did not demonstrate hastening in our PD patients as a whole. First, we used contrast tests to define hastening, while Logigian [25] defined hastening as tapping at frequencies higher than three SD from the mean of the control group. Nakamura [1] and Freeman [15] did not refer to any systematic method to identify hastening, but related it to all tapping at frequencies greater than the cue as hastening. The large variation in average-tapping frequency within our control population made Logigian’s method unjustified. When analyzing our data according to Logigian’s method, we found only two out of all PD patients, as opposed to one control subject with hastening. Alternatively, using the 95% confidence limit criterion, we found that 16 PD subjects and 12 control subjects had hastening.

Hastening, however, might occur in fragments, alternating with the accurate non-hastened rhythm. We could not detect hastening when we looked at the entire tapping time (10 s or more). Because we looked at the mean frequencies and used SD as a measure of variations in time intervals, intercurrent short ‘hastening’ periods could remain undetected when the majority of taps were performed in a non-hastened rhythm. However, the original hastening phenomenon suggested that patients with PD could not maintain a particular frequency because of basic clocking disturbances. Considering short segments of different frequencies on a background of a correct rhythm is probably another dysrhythmic disturbance and not hastening. As a result, we did not analyze the data for short fragments of ‘hastening’.

In terms of tapping frequency, there was only one difference between the PD group and controls PD patients showed bradykinesia in the fastest self-paced practice. That observation could be attributed to the AR and TP subgroups.

Looking at all four paradigms, our results correlate with prior work [15–17] that demonstrate that PD patients perform better when they are given an external pacing.

A potentially confounding factor in our study was the choice of hand tested. Our subjects tapped with the contralateral arm of the most affected limb, in order to limit the effect of motor deficits on the timing tasks. If the non-dominant hand was the less affected side, it could result in a poorer performance unrelated to the disease, since those patients might have tapped more easily and more synchronously with their dominant hand. Indeed, 75% of the PD subjects tapped with their non-dominant hand. If anything, we might have expected more disturbances related to this factor.

The hypothesis behind the present study was that dysrhythmicity and hastening might be different among subgroups of PD patients. The results support this hypothesis: the TP subgroup was the only subgroup to exhibit any evidence of hastening. We suggest that specific pathology might be responsible for the different phenotypic subgroups of PD, and as a result, the groups reacted differently to external rhythm.

Further study is required to determine if one or more specific PD subtypes are associated with differences in rhythm generation, as observed in our study. If so, this could help explain important disease-specific deficits that might shed light on underlying physiological mechanisms and treatment responses. In addition, our finding of hastening in the PD subgroup with tremor might be related specifically to the pathophysiology of this subgroup. Ultimately, this finding could help explain this phenomenon better and hence help us treat patients more effectively.

References


