Poor Dopaminergic Response of Impaired Dexterity in Parkinson’s Disease: Bradykinesia or Limb Kinetic Apraxia?

Andreas Gebhardt, MD,1 Tim Vanbellingen, MSc,1 Fabio Baronti, MD, PhD,1 Bernd Kersten, PhD,2 and Stephan Bohlhalter, MD3

1Parkinson Center, Klinik Bethesda, Tschugg, Switzerland
2Department of Psychology, University of Bern, Bern, Switzerland
3Division of Cognitive and Restorative Neurology, Inselspital, Department of Neurology, Bern University Hospital, Bern, Switzerland

Abstract: Patients with Parkinson’s disease (PD) often show impaired manual dexterity even when being only minimally bradykinetic, suggesting that they may have limb kinetic apraxia (LKA), that is, a loss of fine motor skill not explained by elemental motor deficits. To explore this dissociation, we investigated the differential dopaminergic responsiveness of dexterity and bradykinesia in PD. Twelve patients with PD (4 women, age 64.4 ± 8.3, mean ± SD) and 12 matched healthy controls (64.8 ± 8.9) were tested twice in ON vs. OFF and 1st vs. 2nd trial, respectively. A coin rotation (CR) task was applied to assess dexterity and a finger tapping (FT) task to assess bradykinesia. Performance was followed by video recording and analyzed by measuring the frequency of CR and FT during three 10-second periods. Statistical analysis was done by a mixed factorial design with group (PD vs. controls) as between-subject factor and medication (ON- vs. OFF-state or 1st vs. 2nd trial), task (FT vs. CR), and handedness (dominant vs. nondominant) as within-subject factors. In patients with PD, regardless of hand involved, dopaminergic treatment only mildly improved CR performance, in contrast to the strong increase in FT scores (up to the level of controls), as demonstrated by the significant triple interaction of the factors group, medication, and task (F1,22 = 7.9, P = 0.01; η² = 0.26). Furthermore, CR scores were considerably lower, both in OFF and ON, than in normal controls, pointing to a substantial impairment of dexterity in PD (P < 0.001). In conclusion, impaired manual dexterity showing significantly diminished response to dopaminergic treatment suggests that dextrous deficits in PD are related to LKA rather than bradykinesia. © 2008 Movement Disorder Society

Key words: limb kinetic apraxia; Parkinson’s disease; coin rotation; finger tapping; premotor cortex

Impairment of fine motor control is a frequent complaint in Parkinson’s disease (PD). The patients typically report difficulties with everyday tasks, such as tying laces or buttoning clothing. Other daily challenges are the use of mobile phones, remote controls for TVs, or computer keyboards. The dextrous deficit may be prominent even when motor functioning is reasonably well, that is, when patients are in good ON without disturbing dyskinesias. Therefore, it has been recently suggested that loss of dexterity in PD may qualify for the presence of a motor disorder called limb kinetic apraxia (LKA), which is relatively independent of bradykinesia-rigidity.1 Hugo Liepmann in 1920 first coined the term LKA as loss of fine motor control not explained by elementary motor deficit such as, for instance, weakness or ataxia.2 LKA has been considered as a higher-order motor disorder since it is thought to be based on the dysfunction of premotor areas, which are located upstream to primary motor cortex.3 However, in contrast to other types of apraxia it does not represent a true cognitive-motor disorder with temporal-spatial or conceptual deficits. LKA rather results when the transmission between time-space representations of skilled movements to target areas of motor cortex is interrupted,4,5 thereby adopting an intermediate position between higher-level apraxia.
and elemental motor disorder. LKA is frequently seen in stroke and neurodegenerative disorders, particularly corticobasal degeneration. It is well-known that precise and independent finger movements, which are typically impaired in LKA, are particularly affected in PD. However, these deficits have traditionally not been considered to be limb kinetic apraxia in nature but have been rather attributed to the parkinsonism. Therefore, the concept of LKA in PD remains controversial.

In this study, we chose the coin rotation (CR) and finger tapping (FT) tasks as paradigms for motor assessment. CR represents a measure of both finger dexterity and motor speed. FT mainly registers slowness of motion (bradykinesia), is part of clinical routine assessment and is item 23 of the Unified Parkinson Disease Rating Scale (UPDRS). The aim of this study is to investigate the differential response of dexterity (CR) and bradykinesia (FT) to dopaminergic treatment in patients with PD compared to age-matched normal controls. We hypothesized that dexterity will be considerably less responsive to dopaminergic treatment than bradykinesia supporting the concept of LKA in PD.

SUBJECTS AND METHODS

Subjects

Twelve patients with PD and wearing off fluctuations as well as 12 age- and sex-matched healthy controls participated in the study. Details of demographic and clinical data are listed in Table 1.

Patients were diagnosed with PD according to UK Brain Bank diagnostic criteria and recruited from our specialized Parkinson Center. They were included in the study if stable wearing off fluctuations and/or early morning off were present. Exclusion criteria were significant medical comorbidity or dementia as defined by Mini Mental Status Examination (MMSE) scores below 27. Patients with dyskinesias, tremor, or musculoskeletal disorders interfering with the CR task were also excluded. All subjects were right-handed as assessed by the Edinburgh Handedness Inventory. The total daily dosage of levodopa “equivalent” was determined as follows: 100 mg levodopa = 1 mg cabergoline = 1 mg pramipexole = 1 mg pergolide = 5 mg ropinirole. Written informed consent was obtained from all patients according to the Declaration of Helsinki, 1975.

Motor Assessment: Manual Dexterity and Bradykinesia

Patients were tested during their hospital stay, when medical treatment was optimized, that is, when their regular medication produced a predictable and good ON state. All patients with PD were examined in the morning in the “practically defined OFF” state (at least 12 hours after the last dose of dopaminergic treatment) and in their “best ON” (on average 1.5 to 2 hours after dopaminergic treatment). For the assessment of dexterity, the subjects were instructed to rotate a Swiss 50-Rappen coin (corresponding exactly in size to a US-Nickle) between their thumb, index, and middle finger (CR task). For measurement of bradykinesia they were asked to tap their index finger against the thumb (FT task). Each task was performed as fast as possible and with both hands separately. In the CR task, the limb kinetic deficit is indicated by the reduced number of half turns per time unit and coin drops. The CR scores were calculated according to the following formula:

\[ \text{CR score} = \frac{\text{half turns}}{\left(\text{coin drops} \times 0.1\right)} \times \text{half turns} \]

Since in patients the order of testing in OFF and ON was not counterbalanced, the healthy volunteers were studied twice (within the same day or up to 2 days later) to control for the potential bias of task repetition.

All patients were given a short period of practice before the test started. All trials were videotaped during three periods lasting 10 seconds, for each hand separately. CR and FT alternated as first task from subject to subject. After test performance, the trials were analyzed with VLC media player (Version 0.8.6d Janus (Intel)) in slow motion. CR (half turns) and FT during 10 seconds were counted, respectively. The last half-turn or finger tap of an individual 10-second period was included when at least half of the movement was completed.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 15.0.0; SPSS, Inc. Chicago, IL). We employed a mixed factorial design with group (patients...
with PD vs. normal controls) as between-subject factor and medication (ON- vs. OFF-state and 1st vs. 2nd trial, respectively), task (FT vs. CR), and handedness (dominant vs. nondominant) as $2 \times 2 \times 2$ within-subject factors. In addition, differences of interest in performances either within or between subjects were analyzed using post hoc paired and unpaired $t$-tests, respectively. Finally, we analyzed the potential relationship of disease duration and age with CR task performances by Pearson’s correlation analysis. Levels of significance was set at $P = 0.05$ (two-tailed). All values are expressed as mean $\pm$ SEM (standard error).

RESULTS

None of the patients had tremor in OFF or dyskinesias in ON interfering with the tasks. Two patients had mild dyskinesias of the neck and trunk during the tasks in ON. Overall, in 6 patients mild peak-dose dyskinesias were present in the history.

The main finding of this study was that, regardless of hand involved and taking into account the potential practice effect of task repetition, dopaminergic treatment in patients with PD, in contrast to FT, only slightly improved CR performance, as demonstrated by the significant triple interaction effect of the factors group (PD vs. controls), medication (ON vs. OFF and 1st vs. 2nd trial, respectively), and task (CR vs. FT) ($F_{1,22} = 7.9, P = 0.01; \eta^2 = 0.26$). The findings are depicted in Figure 1.

Assessed by post hoc paired $t$-tests in patients with PD the mild improvement of CR task from OFF to ON state was significant ($P = 0.02$), it was insignificant when analyzed for both hands separately (see Table 2). By contrast, differences in FT scores between OFF and ON were, as expected, highly significant even when each hand was considered alone ($P < 0.001$). The dissociation of CR and FT response to dopaminergic treatment was present in all patients. Performance scores of corresponding 1st and 2nd trials within healthy controls were not different for all experimental conditions.

Post hoc unpaired $t$-tests revealed that the PD patients scored significantly lower in CR task than normal controls, both in ON and OFF, indicating that the impairment of dexterity was substantial ($P < 0.001$; see also Table 2). By contrast, although in ON the FT scores of patients with PD did not reach the level of healthy controls, the difference was not statistically significant ($P = 0.11$). The results of descriptive and $t$-test statistics are summarized in Table 2.

From the factorial analysis further results emerged. As predictable in a right-handed study population, there was a significant main effect of handedness ($F_{1,22} = 6.63; P = 0.02; \eta^2 = 0.23$) indicating that performances were generally better on the right than left side. This was more pronounced in OFF states or first trials, respectively, as shown by the significant interaction handedness by medication ($F_{1,22} = 4.5, P = 0.04, \eta^2 = 0.17$). Furthermore, differences in right and left hand performances were tentatively more pronounced in the CR task of PD patients (CR-L vs. CR-R, see Table 2). However, overall, handedness played a minor role, as all other interactions with handedness did not reach significance. Most importantly, the effect of handedness did not differ between patients and controls, as evidenced by insignificant interactions with the factor group, e.g., the interactions handedness by group ($F_{1,22} = 0.49, P = 0.49; \eta^2 = 0.02$).

In line with the different task demands, both patients and controls performed considerably better in the FT than CR task, which is reflected by the highly significant main effect of task ($F_{1,22} = 120.1, P < 0.001; \eta^2 = 0.85$). High significance could also be detected for the main effect of medication ($F_{1,22} = 19.5, P < 0.001; \eta^2 = 0.7$). However, this medication effect was explained mainly by the better performance in ON of patients with PD as demonstrated by the large interaction of medication and group ($F_{1,22} = 9.8, P = 0.005; \eta^2 = 0.31$).

We finally performed Pearson’s correlation analyses of the CR task performances as a function of age or disease duration. The findings demonstrated a significant negative correlation of age with CR task perform-
TABLE 2. Mean performance scores of patients with PD and age-matched healthy controls

<table>
<thead>
<tr>
<th>Task</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OFF</td>
<td>ON</td>
</tr>
<tr>
<td>CR</td>
<td>5.9 ± 0.6*</td>
<td>6.9 ± 0.7</td>
</tr>
<tr>
<td>CR-L</td>
<td>4.6 ± 0.7</td>
<td>5.5 ± 0.9</td>
</tr>
<tr>
<td>CR-R</td>
<td>7.3 ± 0.9</td>
<td>8.1 ± 0.9</td>
</tr>
<tr>
<td>FT</td>
<td>19.2 ± 2.4**</td>
<td>26.6 ± 2.7**</td>
</tr>
<tr>
<td>FT-L</td>
<td>18.8 ± 2.2</td>
<td>26.7 ± 2.9</td>
</tr>
<tr>
<td>FT-R</td>
<td>20.5 ± 2.6</td>
<td>27.0 ± 2.7</td>
</tr>
</tbody>
</table>

Data shown as mean ± SEM.
*P = 0.02; **P < 0.001, incl. OFF vs. ON of FT-L and –R, all other paired t-tests between OFF vs. ON and 1st vs. 2nd trials were insignificant; §P < 0.001, for all OFF vs. 1st trial conditions and all ON vs. 2nd trial comparisons of CR; §§P = 0.11, incl. insignificant ON vs. 2nd trial comparisons of FT-L and –R.
CR, coin rotation; FT, finger tapping; L, left; R, right.

It is conceivable that abnormal sensorimotor integration, in particular if based on defective kinesthesia as demonstrated during passive movements in PD,16 may contribute to the poor performance in CR and explain in part the deficient response to dopaminergic treatment.17,18

DISCUSSION

Loss of manual dexterity is an important source of disability in PD. The deficit is particularly apparent when manipulating small objects that require the ability to selectively innervate and control individual finger muscles. Loss of this type of independent digital dexterity not explained by elemental motor deficit has been defined as LKA and can be assessed straightforwardly by the CR task.1,6,12 These findings demonstrate that within the group of patients with PD dopaminergic treatment had only little influence on CR scores, while, as expected, clearly improved FT scores by almost 40%. In addition, in line with a previous report,1 a dissociation of strongly reduced CR and almost normal FT scores in ON stage compared with healthy controls could be detected. Some improvement of CR scores in ON was expected, since this task measures both dexterity and motor speed. However, the differential response of finger dexterity and bradykinesia clearly demonstrates that difficulties with dextrous movements are only partially related to elemental, specifically, extrapyramidal deficits. Therefore, the findings support the concept that patients with PD suffer from LKA, which is independent of dopaminergic deficit. Based on the almost normal FT but considerably reduced CR scores in ON the question may arise whether the CR task is simply a much more sensitive measure of bradykinesia than is FT. However, this possibility is unlikely, since bradykinesia as a cardinal sign of PD is typically most responsive to dopaminergic treatment. Moreover, dopaminergic efficacy has been demonstrated to be particularly prominent for the frequently observed extra slowness of complex sequential movements in PD.16

It is conceivable that abnormal sensorimotor integration, in particular if based on defective kinesthesia as demonstrated during passive movements in PD,17,18 may contribute to the poor performance in CR and explain in part the deficient response to dopaminergic treatment.19 The low CR scores may also be reflected by some impairment of interjoint coordination as has been shown by kinematic analysis.20 However, at the clinical level, our patients did not show any sensory abnormality which could account for the deficit in CR. Therefore, although the etiology of dexterity problems in PD is certainly multifaceted, we think the loss of individual digital control measured by CR is best described as LKA.

Recently, significant improvement of both movement time as well as dexterity has been demonstrated with deep brain stimulation (DBS) and/or medication in advanced PD.21 In contrast to this study, dexterity was measured using a rotation task involving only the index finger and thumb, which did not assess segregated finger innervations as required for the CR task. Furthermore, the findings were probably influenced by an additional reduction of tremor and dyskinesias after DBS.

The dextrous disability in our patients was substantial as their mean CR scores were more than 50% below those of healthy controls, irrespective of medication status. CR scores were particularly low for the left hand, which is probably related to the handedness. Nonetheless, handedness did not play greater role in patients than controls as the insignificant interaction of group and handedness demonstrated. The discrepancy is less likely explained by asymmetry of the disease, since in patients, FT scores were only minimally different between left and right hand.

It has been speculated that learned non-use of hands due to long-term bradykinesia-rigidity may underlie the development of LKA in patients with PD.1 Therefore, the LKA may be more pronounced in later stages of the disease. However, in this study, disease duration did not correlate with CR scores. There was a weak negative correlation of dexterity with age on the dominant hand suggesting that limb kinetic impairment may be greater in elderly patients. More studies are needed, though, to clarify the influence of these demographic factors on dexterity in PD.
It has been argued that introducing a new term such as LKA to describe dexterity problems in PD adds little to the current knowledge and elucidation of underlying mechanism.\(^4\)\(^5\) Nonetheless, we think that the concept of LKA in PD may have in fact heuristic implications by providing a model for better understanding of the pathophysiology underlying impaired fine motor skill and ultimately for the prospective of more targeted treatment. LKA is thought to be caused by a disruption of so called innervatory patterns putatively stored in the premotor cortex (PM) including the supplementary motor area (SMA).\(^2\)\(^3\) The innervatory patterns project time-space representations of movements, also known as visuo-kinesthetic engrams, to appropriate targets in downstream primary motor cortex.\(^4\)\(^5\) In a parkinsonian state, innervatory patterns may be dysfunctional due to underactivation of premotor areas. Premotor dysfunction as demonstrated by neuroimaging studies\(^24\)\(^25\) is considered responsible for cardinal parkinsonian motor features such as bradykinesia-rigidity reflecting a cortical deafferentiation within basal ganglia-thalamo-cortical circuits.\(^26\) Accordingly, dopamine depletion in substantia nigra eventually reduces the excitatory thalamocortical input to the lateral PM and SMA as well as to the motor cortex. Hence, premotor dysfunction in PD may represent a common neural basis for both bradykinesia-rigidity and LKA. However, our findings suggest that LKA may be relatively independent of basal ganglia function, since responsiveness of dexterity to dopaminergic treatment is markedly reduced.

The CR task is clearly more demanding with respect to individuated finger use than the FT task. Furthermore, the CR task involves a sensorimotor interaction with an object. It is therefore plausible that motor control during CR relies more on cortical mechanisms. A recent study of recovered patients with pure hemiparesis indicated that the independent movements of thumb and index finger were relatively spared compared with the more ulnar fingers when cortical or corticospinal system was damaged. Hence, the CR task by involving the middle finger may be inherently more vulnerable to cortical dysfunction than FT.

In conclusion, the fact that impaired fine motor skills in PD are only mildly responsive to dopaminergic treatment underscores the importance of neurorehabilitation in the management of dexterity problems. Although conventional occupational therapy improves dexterity in PD, the effects were not maintained\(^26\) and specific treatment approaches for limb kinetic deficits in PD are not available.\(^29\) It is expected that better understanding of neural basis underlying LKA in PD may eventually provide a more rational basis for their rehabilitative treatment.

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