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Original Article

Instrumental analysis of finger tapping reveals a novel early biomarker of parkinsonism in idiopathic rapid eye movement sleep behaviour disorder

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ABSTRACT

Background: Idiopathic rapid eye movement sleep behaviour (iRBD) is considered as a risk factor for Parkinson's disease (PD) development. Evaluation of repetitive movements with finger tapping, which serves as a principal task to measure the extent of bradykinesia in PD, may undercover potential PD patients. The aim of this study was to explore whether finger tapping abnormalities, evaluated with a 3D motion capture system, are already present in RBD patients.
Methods: Finger tapping data was acquired using a contactless 3D motion capture system from 40 RBD subjects and compared to 25 de-novo PD patients and 25 healthy controls. Objective assessment of amplitude decrement, maximum opening velocity and their combination representing finger tapping decrement was performed in the sequence of the first ten tapping movements. The association between instrumental finger tapping data and semi-quantitative clinical evaluation was analyzed.
Results: While significant differences between PD and controls were found for all investigated finger tapping measures ($p < 0.002$), RBD differed from controls in finger tapping amplitude ($p = 0.004$) and velocity ($p = 0.007$) decrement but not in maximal opening velocity. A significant relationship between the motor score from the Movement Disorders Society - Unified Parkinson's Disease Rating Scale and finger tapping decrement was shown for both patient groups, ie RBD ($r = 0.36$, $p = 0.02$) and PD ($r = 0.60$, $p = 0.002$).
Conclusions: In our group of RBD patients we demonstrated amplitude decrement of repetitive movements, which may correspond with prodromal bradykinesia. Our findings suggest instrumental analysis of finger tapping abnormalities as a potential novel clinical marker reflecting subclinical motor disturbances in RBD.

1. Introduction

Idiopathic rapid eye movement sleep behaviour disorder (RBD) manifests with a loss of sleep muscle atonia, and dream-enactment behavior [1]. Recent studies have shown that patients with RBD are at a high risk for conversion into manifest α-synucleinopathy, ie Parkinson's disease (PD), dementia with Lewy bodies, or multiple system atrophy [2,3]. In particular, 33.5% of RBD patients will develop a neurodegenerative disease within five years after diagnosis, 82.4% after 10.5 years and, eventually, up to 96.6% 14 years after diagnosis [4]. This remarkably increased risk of developing overt α-synucleinopathy makes RBD an interesting target for investigating the progress of this prodromal disease with the ultimate goal of finding robust and reliable biomarkers suitable for targeted screening that would aid in identifying subjects at high-risk for developing parkinsonism and dementia [5,6].

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Bradykinesia is considered as the key feature of PD and is used as a general term encompassing not only motor slowness but also poverty of spontaneous movements (akinesia) and reduced amplitude of movements (hypokinesia) [7,8]. The complex nature of bradykinesia makes it difficult to rate its severity in a clinical setting; this is particularly true for mild impairment and untrained examiners [9]. However, a principal feature of bradykinesia called sequence effect, representing the amplitude and velocity decrement during repetitive and continuing movements interferes with routine motor activities and can be evaluated by clinical tests such as the finger-tapping task [10,11]. Therefore, the amplitude reduction during repetitive movements is part of the diagnostic criteria of PD [12], and the finger-tapping test is included in the motor subsection of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scale for the evaluation of PD severity [13]. The examiner is instructed to evaluate the movement of the patient's fingers from the first 10 taps, by using their thumb and index fingers trying to achieve maximum distance between the tips of the fingers as well as keeping the repeated motion as fast as possible.

With the aim to overcome the disadvantage of subjective evaluation and to provide more sensitive continuous measures, several instrumental approaches have been proposed to assess bradykinesia via finger tapping [14–18]. Although these studies showed superior performance in discriminating between PD and healthy controls compared to standard clinical ratings [14–18], identification of different patterns of bradykinesia in the preclinical course of the disease has been limited. From investigated bradykinetic features, slowed finger tapping was apparent in PD cases, as compared to healthy controls, throughout the entire prediagnostic phase beginning up to 15.8 years before clinical diagnosis [19]. However, this study used a very crude semi-quantitative assessment of finger tapping using a self-developed 3-point rating scale [20]. A recent pioneering study showed promising accuracy of instrumental preclinical motor assessment via the finger tapping test in differentiating between healthy controls and patients with idiopathic hyposmia [20], as the presence of hyposmia is associated with 6.5 higher likelihood ratio for developing PD [21]. Although it is well-known that the quantitative motor tests are very strong predictors of conversion to synucleinopathy with one of the greatest hazard ratios [22], the reliability of instrumental finger tapping assessment as a potential early diagnostic marker of parkinsonism has never been investigated in RBD.

Therefore, we aimed to utilize a contactless motion capture system to record the finger tapping in RBD patients, de-novo PD patients and healthy controls, with at goal to verify whether finger tapping abnormalities are detectable in RBD and whether these abnormalities are similar to those found in early PD.

2. Methods

2.1. Participants

From 2015 to 2019, 25 patients (5 F, 20 M) with PD, mean age 65 ± 8 yrs, 40 patients (5F, 35M) with idiopathic RBD, mean age 66 ± 6 yrs, and 25 healthy controls (CON) (3 F, 22 M), mean age 66 ± 7 were recruited (Table 1). All de-novo, drug-naive PD patients were diagnosed in accordance with the MDS clinical diagnostic criteria for PD [12]. The RBD diagnosis was confirmed by video-polysomnography according to the International Classification of Sleep Disorders, third edition (ICSD-3) [23]. For inclusion, RBD patients had to be older than 49 years without overt parkinsonism, dementia, as well as factors indicative of secondary RBD such as narcolepsy, drug-induced RBD (ie RBD originating shortly after initiation of antidepressants), or focal brainstem lesions on MRI. Control subjects (CON) were recruited from the general community through advertisements. To be eligible for the study, controls had to be free of major neurologic disorders, active oncologic illness, and abuse of psychoactive substances. In all control subjects, RBD was excluded by thorough history and video-polysomnography. All subjects were scored according to the MDS-UPDRS III motor score (ranging from 0 to 132, with 0 for no motor manifestations and 132 representing severe motor distortion) by a MDS certified rater. The finger tapping item subscore of the MDS-UPDRS III was estimated as the average performance of both hands, ranging from 0 to 4 with 0 for no problem and 4 representing the inability to perform the task because of slowing, interruptions or decrements. Additionally, cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) score. All participants gave their informed consent to participate in the study. The study was approved by the Ethics Committee of the General University Hospital in Prague, Czech Republic, and therefore performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

2.2. Finger tapping instrumental analysis

In the subsequent independent evaluation, that was not part of the original MDS-UPDRS III scoring performed by neurologist, all subjects performed finger tapping test according to MDS-UPDRS instructions, while the movements were recorded by a contactless 3D motion capture system (V120: Trio, Optitrack) and analysed with BradykAn software (Suppl. Video S1) [24]. The first 10 finger taps were retained for subsequent analysis in accordance with the MDS-UPDRS instructions. The system continuously tracked the mutual distance of markers placed on the distal phalanx of the thumb and forefinger. Finger tapping distance signal was normalized to the maximum opening distance. Based on previous studies [18,25], we calculated three fundamental parameters for evaluation of the sequence effect and slowness of movement: amplitude decrement (AD), maximum opening velocity (OV) and finger tapping decrement (FTD) representing the combination of AD and OV. AD is defined as the mean slope of the regression lines interlaced within five subsequent peaks when only negative slopes are considered; ie maximum of six regression lines beginning at peaks one to six are averaged (Fig. 1A). OV is defined as the mean slope of tangents of maximum opening velocity minus 90° (Fig. 1B). FTD is defined as the mean sums of AD and respectively OV when only negative AD are considered (Fig. 1C). As all angle values are negative, the results are shown as absolute values. Each hand was measured twice and the results were averaged to reduce potential variability. Since it is difficult to identify the more affected side in RBD patients due to only subclinical changes in finger tapping performance, the results of both hands of every subject were averaged for subsequent analysis.

Supplementary video related to this article can be found at doi:10.1016/j.sleep.2020.07.019.

2.3. Statistics

Distributions of finger tapping parameters were tested using the Kolmogorov–Smirnov normality test. Since the finger tapping parameters were normally distributed, groupwise comparisons were done by analysis of variance with post-hoc Fisher least-squares difference. Bonferroni correction for multiple comparisons was applied resulting in a minimal significant p-value threshold of 0.017 (ie, 0.05/3 for three performed tests). Receiver operating characteristic (ROC) and its area under curve (AUC) were computed. Sensitivity and specificity was determined as the optimal operating point of the ROC curve. As the clinical ratings in the RBD group represent a rather ordinal scale, the relationships between clinical

scores and FTD was analysed by the Spearman correlation test. The correlation between finger tapping performance subscore and FTD could be analysed only in the PD group due to the wider range of bradykinesia severity.

3. Results

Analysis of variance showed significant group differences across all three parameters of AD, OV and FTD ($p < 0.017$). RBD differed from CON in AD ($p = 0.004$) and FTD ($p = 0.007$). The differences between PD and CON groups were found for AD ($p = 0.002$), OV ($p < 0.001$), and FTD ($p < 0.001$). There was also a significant difference between PD and RBD in OV ($p < 0.001$) and FTD ($p < 0.001$) (Fig. 2).

In the outcome of the analysis represented by FTD, we found a discrimination accuracy of AUC 0.75 (sensitivity 76%, specificity 63%) between RBD and CON, AUC 0.82 (sensitivity 80%, specificity 72%) between PD and CON, and additionally AUC 0.67 (sensitivity 68%, specificity 60%) between PD and RBD. Admittedly, we were able to discriminate RBD from CON based solely on AD with AUC 0.80 (sensitivity 72%, specificity 80%).

A significant relationship between the MDS-UPDRS III score and FTD was revealed for both patient groups, RBD ($r = 0.36$, $p = 0.02$) as well as PD ($r = 0.60$, $p = 0.002$). In PD group, significant positive correlation between the MDS-UPDRS III finger tapping item subscore and FTD was also found ($r = 0.54$, $p = 0.006$). In addition, a relationship between MoCA and FTD was detected in RBD ($r = -0.51$, $p < 0.001$), but not in PD and HC groups. No relationship between FTD and age was seen.

4. Discussion

Based on the objective 3D motion capture system, the current study revealed for the first time the presence of finger tapping abnormalities in RBD. Since the instrumental finger tapping performance in our RBD cohort intermediated between de-novo PD and healthy controls and since RBD is considered as a prodromal stage of PD and other synucleinopathies [2,3], we assumed that observed changes in repetitive finger movements might represent a prodromal marker of neurodegeneration. This has been further supported by the observed correlations between the motor part of MDS-UPDRS score and instrumental analysis of finger tapping decrement in RBD. Our findings are thus in agreement with recent research suggesting that PD patients manifest finger tapping abnormalities throughout the prediagnostic phase [19] and that the sequence effect may be most prominent in the early stages of PD [17]. Interestingly, we detected a relationship between MoCA scores and finger tapping decrement in the RBD group. Although the mean MoCA score was only slightly decreased in RBD patients compared to controls, the observed relationship might correspond to previous observations showing that cognitive decline is a progression marker in RBD [26].

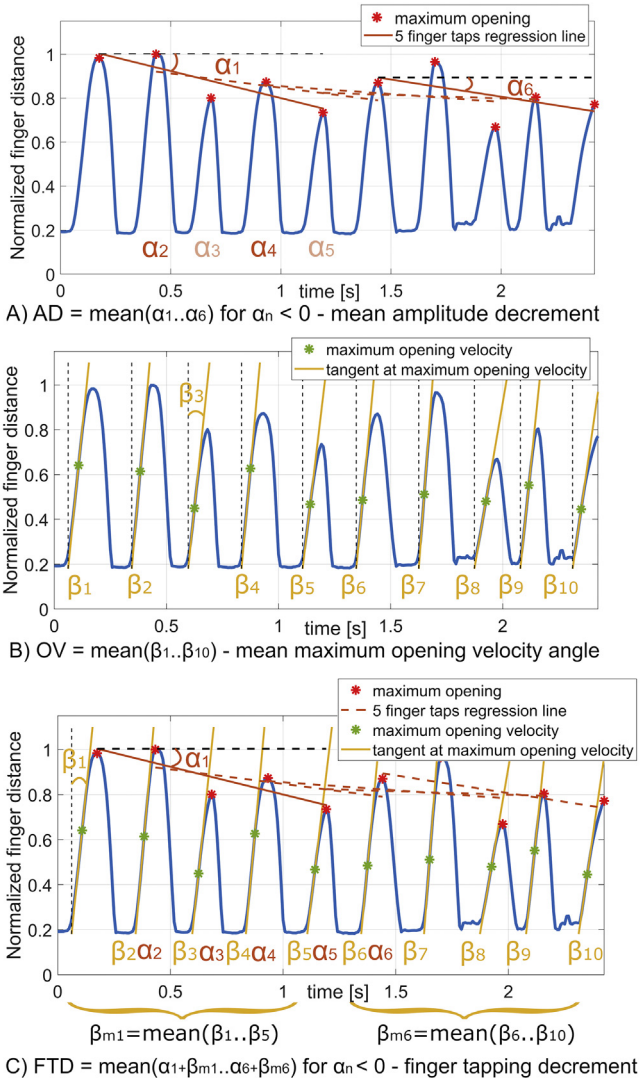

Fig. 1. Principle of instrumental finger tapping parameters computation on selected 10 amplitudes of finger tapps including (A) mean amplitude decrement angle, (B) mean maximum opening velocity angle, and (C) mean finger tapping decrement.

Table 1
Clinical characteristics of participants.

	CON (n = 25)	RBD (n = 40)	PD (n = 25)	P-value
Mean Age (years)	66 (SD 7, range 51–81)	68 (SD 6, range 53–80)	65 (SD 8, range 51–81)	0.32
Men	88% (n = 22)	88% (n = 35)	80% (n = 20)	–
MDS-UPDRS III	2.5 (SD 1.9)	9.0 (SD 4.8)	30.2 (SD 13.3)	<0.001[a,b,c]
MDS-UPDRS III - finger tapping item subscore (mean left, right)	0.08 (SD 0.24)	0.38 (SD 0.46)	1.64 (SD 1.02)	<0.001[b,c]
MoCA	25.8 (SD 1.5)	24.6 (SD 4.8)	25.0 (SD 2.8)	0.73
Duration of RBD/PD symptoms	–	5.4 (SD 4.1)	1.4 (SD 1.0)	–
Clonazepam therapy	0% (n = 0)	45% (n = 18)	0% (n = 0)	–
RBD presence	0% (n = 0)	100% (n = 40)	32% (n = 8)	–
Antidepressant therapy	4% (n = 1)	25% (n = 10)	12% (n = 3)	–
Antiparkinsonian therapy	0% (n = 0)	0% (n = 0)	0% (n = 0)	–

SD = standard deviation, PD = Parkinson's disease, RBD = rapid eye movement sleep behaviour disorder, CON = Controls, MDS-UPDRS = Movement Disorder Society - sponsored revision of the Unified Parkinson's Disease Rating Scale. Kruskal–Wallis test: [a]significant difference between CON and RBD; [b]significant difference between CON and PD; [c]significant difference between RBD and PD.

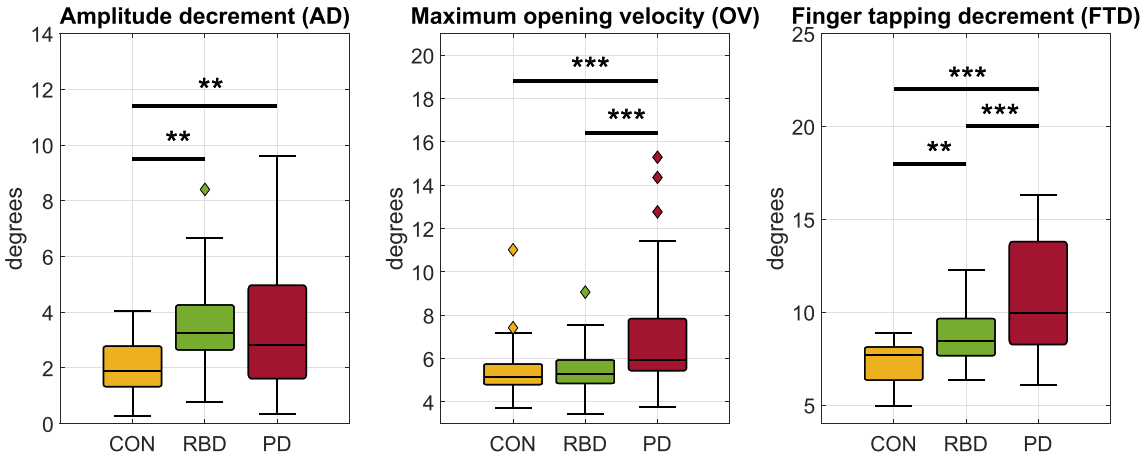

Fig. 2. Box plots of finger tapping characteristics. Analysis of variance with Bonferroni adjustment was used to test for group differences with: **p < 0.01 and ***p < 0.001.

The instrumental finger tapping analysis showed the largest discriminative ability with AUC of 0.82 between newly diagnosed PD patients and healthy controls. In general, these results are similar to sensitivity and specificity of a finger tapping test in discriminating between PD and healthy controls reported in previous studies [14–18]. The partial overlap between PD and healthy controls is also in line with previous experience showing that 16% of individuals without parkinsonism have a MDS-UPDRS motor score of 10 or more. The burden of parkinsonian motor signs in the population is associated with older age, the female sex, osteoarthritis, and diabetes mellitus [27]. Importantly, in contrast to clinical examination assessing the presence of several symptoms, a large discrimination ability in this study was achieved using a single parameter of finger tapping decrement, which was designed to reflect both amplitude decrement and decrease of maximum opening velocity, the two fundamental features of bradykinesia in PD [11]. While progressive decrement of amplitude during repetitive movements reflects the sequence effect [12], reduced opening velocity can be associated with slowness of movements [14] and can be related to changes in the finger tapping rhythm [28].

Similar to de-novo PD, our RBD cohort also manifested a significant finger tapping decrement detectable by instrumental analysis. However, the most prominent discriminative accuracy of the AUC was up to 0.80 between RBD and healthy control groups was demonstrated by amplitude decrement, while the opening velocity was not affected in RBD. This interesting finding might imply that prodromal bradykinesia in PD starts with changes in amplitude, followed by motor slowing. Nevertheless, this phenomenon has yet to be confirmed by future longitudinal studies.

To evaluate bradykinesia and especially sequence effect, we chose the finger tapping test because it was shown that the sequence effect in PD is more prominent in individual than in non-individual finger movements [16]. However, the alteration of finger tapping performance in RBD was not clinically detectable using MDS-UPDRS III finger tapping item subscore, where the score of RBD was only slightly but not significantly increased compared to the performance of healthy controls. For the same reason, it was not possible to determine the more affected side in the RBD cohort. Therefore, the average performance of both hands was preferred for subsequent statistical analyses. Although not performed during the same session, we were still able to find a moderately strong relationship between neurological and instrumental evaluation of finger tapping in PD, indicating a sufficient reliability of 3D motion capture systems in detecting the finger tapping decrement as compared to an experienced rater.

5. Conclusion

This study demonstrated the presence of the sequence effect in RBD patients and therefore broaden the range of clinical markers reflecting initial motor disturbances in RBD. The instrumental examination of finger tapping may have the potential to provide a new tool for researching neurodegenerative synucleinopathies, as the revealed sensitivity appears to be comparable or superior to other prodromal motor markers based on instrumental analysis such as speech, eye movements, gait, and postural stability [29–31]. Moreover, 3D motion capture cameras provided actual values measured in space and time, allowing computation of the principal characteristics of bradykinesia and studying even small changes in associated phenomena such as the sequence effect. Future longitudinal studies are necessary to estimate the reliability of instrumental analysis of finger tapping to predict conversion of iRBD into manifest parkinsonism.

CRediT authorship contribution statement

Radim Krupička: Conceptualization, Methodology, Software, Writing - original draft, Writing - review & editing, Visualization. **Petr Krýže:** Software, Writing - original draft. **Slávka Neťuková:** Software, Validation, Formal analysis. **Tereza Duspivová:** Formal analysis. **Ondřej Klempíř:** Validation, Formal analysis. **Zoltán Szabó:** Validation, Resources, Writing - review & editing, Supervision. **Petr Dušek:** Conceptualization, Validation, Resources, Writing - review & editing. **Karel Šonka:** Conceptualization, Resources, Writing - review & editing. **Jan Rusz:** Conceptualization, Methodology, Validation, Formal analysis, Writing - original draft, Writing - review & editing, Supervision. **Evžen Růžička:** Conceptualization, Methodology, Validation, Resources, Writing - review & editing, Supervision.

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Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.07.019.

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