Parkinsonism and Related Disorders 94 (2022) 45–48

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Short communication

Shannon entropy: A novel parameter for quantifying pentagon copying performance in non-demented Parkinson's disease patients

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ARTICLE INFO

Keywords:
Parkinson's disease
Kinematic analysis
Pentagon copying test
In-air movement
Shannon entropy

ABSTRACT

Introduction: Impaired copy of intersecting pentagons from the Mini-Mental State Examination (MMSE), has been used to assess dementia in Parkinson's disease (PD). We used a digitizing tablet during the pentagon copying test (PCT) as a potential tool for evaluating early cognitive deficits in PD without major cognitive impairment. We also aimed to uncover the neural correlates of the identified parameters using whole-brain magnetic resonance imaging (MRI).

Methods: We enrolled 27 patients with PD without major cognitive impairment and 25 age-matched healthy controls (HC). We focused on drawing parameters using a digitizing tablet. Parameters with between-group differences were correlated with cognitive outcomes and were used as covariates in the whole-brain voxel-wise analysis using voxel-based morphometry; familywise error (FWE) threshold $p < 0.001$.

Results: PD patients differed from HC in attention domain z-scores ($p < 0.0001$). In terms of tablet parameters, the groups differed in Shannon entropy (horizontal in-air, $p = 0.003$), which quantifies the movements between two strokes. In PD, a correlation was found between the median of Shannon entropy (horizontal in-air) and attention z-scores ($R = -0.55$, $p = 0.006$). The VBM revealed an association between our drawing parameter of interest and gray matter (GM) volume variability in the right superior parietal lobe (SPL).

Conclusion: Using a digitizing tablet during the PCT, we identified a novel entropy-based parameter that differed between the nondemented PD and HC groups. This in-air parameter correlated with the level of attention and was linked to GM volume variability of the region engaged in spatial attention.

1. Introduction

Subtle cognitive deficits are very common in Parkinson's disease (PD) and mostly include altered attention and executive functions that are particularly related to dopaminergic deficits and dysfunction of association basal ganglia circuitry [1], although other neurotransmitters seem to be involved as well [2]. In addition to the abovementioned profile of cognitive impairment, other cognitive domains may be affected [3]. For a quick and easy assessment of executive and visuospatial functions, a task involving copying two intersecting pentagons is often used. Performance in the pentagon copying test (PCT) has been shown to predict cognitive decline in PD [4]; however, results may vary depending on the scoring method [5]. We have shown that handwriting kinematic parameters, assessed with the help of a digitizing tablet, can precisely quantify both "on-surface" and "in-air" hand movements [6], and the in-air kinematic parameters distinguished PD from healthy controls (HC) with higher accuracy than the well-described on-surface handwriting parameters [7]. Hesitation and uncertainty between two handwriting/drawing strokes lead to excessive in-air movements that may reflect disturbed planning of movement execution and/or cognitive deficits. We have previously shown that Shannon entropy, i.e. a numerical measure of the randomness or uncertainty of a signal, is a good in-air parameter that reflects alterations of PD handwriting [8]. Therefore, in the frame of this study, using a digitizing tablet and exploiting the Shannon entropy, we aimed to identify a more precise parameter that would quantify PCT and distinguish nondemented PD subjects from

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https://doi.org/10.1016/j.parkreldis.2021.11.037
Received 15 September 2021; Received in revised form 8 November 2021; Accepted 30 November 2021
Available online 4 December 2021

HC. We also aimed at identifying their cognitive and neural correlates.

2. Methods

2.1. Participants

We enrolled 27 patients with clinically established PD and 25 HC. All participants were right-handed. None of the subjects had a history or presence of psychosis, hallucinations, depression, or dementia [3]. All PD patients were on a stable dopaminergic medication and were tested in the ON medication state without dyskinesias. All participants signed an informed consent form that was approved by the local ethics committee.

2.2. PCT parameters and visual scoring

The participants were asked to perform a drawing on an A4 paper that was laid down and fixed to a digitizing tablet Wacom Intuos 4 M. Collected signals are described in Suppl. Material.

During the parameterization of the PCT drawings, we focused on six features included in evaluating the on-surface drawing: 1) spatial features – height and length; 2) temporal feature – duration of drawing; 3) kinematic feature – relative standard deviation of acceleration which is associated with the fluency of drawing; and 4) entropy-based features – median of Shannon entropy extracted from in-air hand movements (horizontal, vertical) between consecutive strokes. A stroke is a product of a drawing on paper performed between two pen elevations, e.g. see the blue lines in Fig. 1 and Suppl. Material for more details. Considering that the horizontal in-air movement is represented by time-series X with n unique samples x_i, then its Shannon entropy is calculated as $H(X) = -\sum_{i=1}^{n} p(x_i) log_2 p(x_i)$, where $p(x_i)$ is the probability density function [8]. Analogically, the formula can be applied to the time series of the vertical in-air movement.

The PCT was scored by a psychologist (LB), using the qualitative scoring of pentagon test (QSPT) method [9]. The total score ranged from 0 to 13 points; for details see the Supplementary materials.

2.3. Neuropsychological assessment

Four cognitive domains (visuospatial, memory, attention, and executive domains) were examined using a complex neuropsychological assessment. The cognitive domain z-scores were computed as the average z-scores of the tests included in the particular domain and were correlated with PCT parameters. For details see the Supplementary materials.

2.4. MRI sequences

Subjects were scanned with a 3T Siemens Prisma MR scanner (Siemens, Erlangen, Germany). High-resolution anatomical T1-weighted images were acquired (TR = 2300 ms, TE = 2.33 ms, FA = 8°, FOV = 224 mm, slice thickness 1 mm, 240 sagittal slices, matrix size 224 × 224).

2.5. Association between PCT parameters and regional GM volumes

SPM12 software was used to pre-process anatomical T1-weighted images. MR images were segmented into gray and white matter segments and the DARTEL imported versions of GM and white matter were obtained for each subject. They were then spatially registered to the MNI coordinate system using the DARTEL toolbox [10]. GM probability maps were Jacobian-modulated in order to preserve the original GM volume and smoothed using a spatial filter with the Gaussian kernel (FWHM = 10 mm). Lastly, the values of images were divided by total intracranial volume (TIV) to correct for the effects of overall brain size. In the second-level whole-brain voxel-wise analysis, we investigated the presence of significant linear correlations between regional volumes and drawing features of interest (i.e. with significant differences between both groups) using the general linear model separately in the HC and PD groups. Age, gender, education, and levodopa equivalent dose (LED) were included as covariates of no interest. Results were considered significant if $p < 0.05$ after FWE correction was performed with the initial threshold being $p < 0.001$.

2.6. Statistical analysis

We used the Mann-Whitney U test to assess differences between HC and PD in PCT parameters, cognitive domain z-scores, and PCT visual scores. Spearman's correlations between PCT parameters of interest (i.e. with significant differences between both groups) and cognitive domains z-scores and PCT visual scores were calculated separately in the PD and HC groups. Additional partial correlation analyses were performed with LED and Unified Parkinson's Disease Rating Scale III (UPDRS III) scores as covariates in order to regress out the effects of motor impairment and/or dopaminergic medication. Bonferroni correction was used to control for multiple testing.

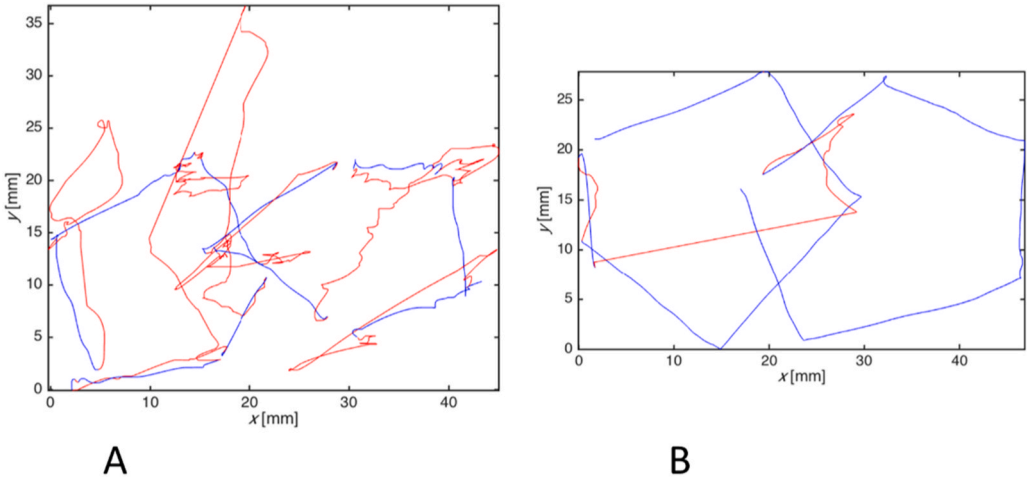

Fig. 1. PCT performed by a PD patient (A) and a HC subject (B). The blue line represents on-surface (on-paper) movement and the red line the in-air one. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3. Results

3.1. Clinical and cognitive outcomes

All 52 subjects completed the study. Altogether 13 patients had left-sided PD symptom predominance, 10 had right-sided symptom predominance, and 4 had bilateral PD. For the demographic and clinical/cognitive data for PD and HC groups, see Table 1. The PD and HC groups differed in all cognitive domains, but only the attention cognitive domain z-scores survived Bonferroni correction (for four measurements). Only 3 out of 27 PD patients had z-scores lower than −1.5 in at least two cognitive tests in one or more cognitive domains and were classified as PD-MCI [3]. The groups slightly differed in the QSPT ($p = 0.016$); however, as expected in non-demented subjects, the scores in both the HC and PD groups displayed a ceiling effect, therefore reducing variability in the data. These significant differences also remained after removal of these 3 subjects (see Suppl. Materials). There were no significant differences between right and left sided dominant patients, see Supplementary Table S4.

3.2. PCT parameters

We observed a significant difference between the HC and PD groups in the median of Shannon entropy (horizontal in-air) ($p = 0.003$), median of Shannon entropy (vertical in-air) ($p = 0.044$), and relative STD of acceleration (on-surface) ($p = 0.014$); see Table 1. Only the Shannon entropy (horizontal in-air) survived the Bonferroni correction for six measurements. For an illustration of in-air movements in PD and HC, see Fig. 1 A,B.

Table 1
Demographic and clinical/cognitive variables.

	PD, N = 27	HC, N = 25	Mann-Whitney
Gender (M/F)	17/10	7/18	p = 0.012
Age (years)	Med. = 67.0 IQR = 11.0	Med. = 67.1 IQR = 7.12	p = 0.806
Education (years)	Med. = 13 IQR = 5	Med. = 17 IQR = 5	p = 0.273
MOCA	Med. = 26 IQR = 6	Med. = 28 IQR = 4	p = 0.019
PD duration (years)	Med. = 4.0 IQR = 8.0	NA	NA
LED (mg)	Med. = 960.0 IQR = 910.0	NA	NA
UPDRS III	Med. = 11.0 IQR = 9.0	NA	NA
Memory domain z-scores	Med. = 0.475 IQR = 1.35	Med. = 1.058 IQR = 1.34	p = 0.033
Attention domain z-scores	Med. = −0.47 IQR = 0.74	Med. = 0.33 IQR = 0.57	p < 0.0001
Executive domain z-scores	Med. = −0.11 IQR = 0.90	Med. = 0.27 IQR = 0.76	p = 0.030
Language domain z-scores	Med. = −0.25 IQR = 1.5	Med. = 0.50 IQR = 1.13	p = 0.014
Visuospatial domain z-scores	Med. = 0.36 IQR = 1.16	Med. = 0.78 IQR = 0.47	p = 0.020
Height of drawing (mm)	Med. = 32.64 IQR = 6.83	Med. = 35.21 IQR = 11.06	p = 0.489
Length of drawing (mm)	Med. = 327.3 IQR = 136.2	Med. = 349.0 IQR = 96.2	p = 0.749
Duration of drawing (s)	Med. = 21.85 IQR = 9.13	Med. = 17.43 IQR = 15.62	p = 0.403
relative STD of acceleration (on-surface) higher values associated with more dysfluent movement	Med. = 20.01 IQR = 10.76	Med. = 14.91 IQR = 5.56	p = 0.014
median of Shannon entropy (horizontal in-air) higher values associated with excessive movements in-air	Med. = 5.4 IQR = 1.12	Med. = 4.54 IQR = 0.95	p = 0.003
median of Shannon entropy (vertical in-air) higher values associated with excessive movements in-air	Med. = 5.37 IQR = 1.23	Med. = 4.56 IQR = 0.92	p = 0.044
QSPT	Med. = 12.0 IQR = 1.0	Med. = 13.0 IQR = 1.5	p = 0.016

Med. – median, IQR – interquartile range.

3.3. Correlation analyses between PCT parameter of interest and cognitive outcomes

In the PD group, we found a significant correlation between the median of Shannon entropy (horizontal in-air) and attention domain z-scores ($R = -0.554$, $p = 0.006$). The result survived Bonferroni correction for four measurements (four cognitive domains z-scores), see Fig. S1 and Table S1 in the Supplementary materials. Similar results were found after regressing out the effects of LED and UPDRS III Motor Assessment ($R = -0.668$, $p = 0.005$).

In the HC group, we found significant correlation between median of Shannon entropy (horizontal in-air) and executive domain z-scores ($R = -0.447$, $p = 0.042$). The result lost significance after correction for multiple testing.

No significant correlations were found between visual PCT scores and cognitive domains in either PD or HC groups; see Table S2 in the Supplementary materials. No association was found between visual PCT scores and the median of Shannon entropy (horizontal in-air) either ($R = 0.096$; $p = 0.697$).

3.4. Correlation between MRI regional GM volumes and PCT parameters of interest

In the PD group, we found a significant negative correlation between our PCT parameter of interest (median of Shannon entropy, horizontal in-air) and GM volume in the right SPL (Brodmann area 7; Cluster size 585 voxels; MNI coordinates 25.5 –64.5 39.0; $p = 0.001$; see Fig. S2 in the Supplementary materials). In the HC group, there were no significant correlations between regional GM volumes and drawing features.

4. Discussion

Our study demonstrated that Shannon entropy extracted from in-air movement between two consecutive strokes, significantly differed between non-demented PD and HC while drawing intersecting pentagons.

Shannon entropy quantifies excessive in-air movements that could be associated with the following activities: movement preparation, in-air motor start hesitation, and movement uncertainty, as well as cognitive impairment or lapses of attention. Previous research focused on handwriting showed more alterations in the horizontal direction of handwriting than in the vertical direction, which may be due to wrist extension stiffness in PD [7,11]. We showed that the variability of horizontal Shannon entropy was closely linked to the level of attention, even after regressing out the effects of motor impairment as assessed by motor score and LED. Attention had been clearly affected in our non-demented PD subjects when compared to HC despite the fact that only 3 out of 27 PD subjects met the criteria for PD-MCI [3] and these significant differences also remained after removal of these 3 subjects. Notably, this correlation was not found with the visual PCT scores, probably due to the ceiling effect and low variability of visual PCT scores in non-demented subjects. We did not find any significant difference between right and left sided dominant patients.

Few studies have focused on assessing the neural correlates of pentagon drawing in PD, with variable results. Filoteo et al. [5] found that PCT accuracy, based on their modified visual scoring system (scores ranged from 3 to 0), significantly correlated with cortical volume variability in the left rostral middle frontal cortex, the right supplementary motor area, the pars triangularis, and the left cuneus in PD patients, i.e. regions involved in the frontoparietal, motor, language, and visual

networks, respectively. Another study by Garcia-Diaz et al. [12] used cortical thickness measures and found that PD patients with abnormal pentagon drawings, as assessed visually, had significant cortical thinning of the right precentral and postcentral gyri, superior parietal region, and posterior cingulate cortex, i.e., in regions linked to higher order visual processing as well as attention and movement execution. Unlike in our study, the PCT scores were associated with widespread cortical region atrophy, meaning that visual PCT scores cannot identify and monitor early brain changes.

We demonstrated that changes in our in-air PCT parameter of interest were significantly related to GM volume variability solely of the right SPL. This region is a part of the dorsal attention network (DAN) [13] as well as the dorsal visual stream. Both pathways are involved in visual (spatial) attention control in PD [13] and atrophic changes of the SPL have been demonstrated early in the course of the disease [14]. Therefore, we assume that disrupted in-air movements during PCT, as assessed by the digitizing tablet, could be an early manifestation of attention-related posterior cortical volume changes that have been shown to predict cognitive decline during the PD course [4]. Future prospective longitudinal studies should assess whether this parameter may serve as an early marker of cognitive impairment and dementia in PD.

In conclusion, we identified a novel in-air parameter for quantitative PCT assessment. This parameter is closely linked to attention levels and to the GM volume variability of the posterior cortical region engaged in both visual attention and visual-spatial processing. Our results indicate that this in-air parameter could be used to evaluate early cognitive changes that precede disturbed pentagon drawing (as assessed visually) and this may be clinically relevant. Future longitudinal studies should assess whether the Shannon entropy of in-air movement will become a good marker for MCI and dementia conversion in PD.

Acknowledgement

This project received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement no. 734718 (CoBeN), from a grant from the Czech Ministry of Health, NU20-04-00294 and Spanish grant Ministerio de ciencia e innovación PID2020-113242RB-I00. We also acknowledge the core facility MAFIL of CEITEC supported by the MEYS CR (LM2018129 Czech-BioImaging).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.11.037.

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