Journal of Neurology (2019) 266:1376–1382
https://doi.org/10.1007/s00415-019-09268-2

ORIGINAL COMMUNICATION

Effect of levodopa on handwriting tasks of different complexity in Parkinson's disease: a kinematic study

Poonam Zham[1] · Dinesh Kumar[1] · Rekha Viswanthan[1] · Kit Wong[2] · Kanae J. Nagao[2] · Sridhar Poosapadi Arjunan[1] · Sanjay Raghav[1,2] · Peter Kempster[2]

Received: 14 December 2018 / Revised: 27 February 2019 / Accepted: 4 March 2019 / Published online: 15 March 2019

Abstract

Levodopa treatment does improve Parkinson's disease (PD) dysgraphia, but previous research is not in agreement about which aspects are most responsive. This study investigated the effect of levodopa on the kinematics of writing. Twenty-four patients with PD of less than 10 years duration and 25 age-matched controls were recruited. A practically defined *off* state method was used to assess the levodopa motor response, measured on the Unified Parkinson's Disease Rating Scale Part III. The kinematic features for six handwriting tasks involving different levels of complexity were recorded from PD patients in off and on states and from the control group. Levodopa is effective for simple writing activities involving repetition of letters, denoting improved fine motor control. But the same benefit was not seen for copying a sentence and a written category fluency test, tasks that carry memory and cognitive loads. We also found significant differences in kinematic features between control participants and PD patients, for all tasks and in both on and off states. Serial testing of handwriting in patients known to be at risk for developing PD might prove to be an effective biomarker for cell loss in the substantia nigra and the associated dopamine deficiency. We recommend using a panel of writing tasks including sentence copying and memory dependence. Dual-task effects may make these activities more sensitive to early motor deficits, while their weaker levodopa responsiveness would cause them to be more stable indicators of motor progression once symptomatic treatment has been commenced.

Keywords Parkinson's disease · Levodopa · Kinematic · Dysgraphia

Introduction

Handwriting is a highly skilled rhythmic fine motor activity, which acquires automaticity through overlearning. For these reasons, it is particularly susceptible to the motor disturbance of Parkinson's disease (PD). Micrographia, defined by Kinnear Wilson as a reduction of the size of lettering in relation to pre-morbid calligraphy [1], is the best recognized parkinsonian writing disorder and is present in 50–60% of PD patients [2].

Computerized graphics tablets can analyze the dynamic aspects of writing, revealing abnormalities that are invisible to pen-and-paper methods. Alterations in velocity, acceleration and fluency are as important as reduced static script size, and the term PD dysgraphia has been proposed to encompass all of these deficits [3]. It has been suggested that kinematic measures of handwriting and drawing are sensitive enough to detect early signs of PD [4]. Using computerized handwriting techniques, it may therefore be possible to identify the first evidence of a parkinsonian motor deficit in at-risk patients (genetically predisposed, or diagnosed with rapid eye movement sleep behavior disorder), increasing the early disease period available for treatment or clinical trials of possible neuroprotective drugs [5]. Thereafter, kinematic writing parameters could augment global motor disability scoring in tracking the motor decline [6, 7].

Responsiveness of PD dysgraphia to dopaminergic drugs is important to a disease monitoring role for computerized writing. Although medication effects have not always been considered in previous handwriting research [5, 6], a number of studies have tested handwriting with and without dopaminergic drugs. While these have shown that

✉ Dinesh Kumar
dinesh@rmit.edu.au

[1] School of Engineering, RMIT University, 3000 Melbourne, Australia

[2] Monash Medical Centre, Melbourne, Australia

anti-parkinsonian treatment does improve writing, there is lack of agreement about which aspects are most responsive.

Cobbah et al. gave levodopa and apomorphine test doses to six PD patients and found improvement in the velocity and acceleration of pen strokes [8]. Eichhorn et al. observed that various kinematic parameters of writing responded to apomorphine when a good overall motor response was present [9]. Tucha et al. noted that levodopa administration results in a partial restoration of automatic movement execution for writing [10]. In the study by Poluha et al., levodopa improved stroke speed without enlarging script size [11]. Broeder et al. showed that dual-task conditions with additional cognitive loading reduced writing amplitude in PD patients but not controls [12].

A shortcoming in some earlier studies has been their restricted handwriting tasks, commonly confined to the repetition of a few letters such as 'e' and 'l'. This approach does not separate improvements in primary motor control from the better execution of complex or concurrent tasks. We aimed to study the change in kinematics of writing in PD patients with treatment using levodopa across a range of activities that required increasing degrees of motor and cognitive processing. An additional objective was to quantify the effect of levodopa by means of a practically defined off state and test dose method. It was our hypothesis that levodopa improves handwriting kinematics for simple writing tasks more than for those associated with cognitive loading or simultaneous action.

Materials and methods

Participants

Twenty-four patients diagnosed with PD within the last 10 years were recruited from the Movement Disorders Clinic at Monash Medical Centre. All complied with the Queen Square Brain Bank criteria for idiopathic PD [13]. The presence of any advanced disease clinical milestones i.e., visual hallucinations, frequent falling, cognitive disability, need for institutional care were exclusion criteria [14]. There were 25 healthy age-matched controls with no neurological or musculoskeletal abnormalities. Each PD subject's usual morning levodopa was administered in a practically defined off state (fasting, with anti-parkinsonian medication withheld for at least 12 h). The on state was taken to be the maximum improvement over the subsequent 30–90 min. Motor function in off and on states was scored by a neurologist on the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) [15]. The cognitive screening was performed using the Montreal Cognitive Assessment (MoCA) [16]. Levodopa equivalent daily doses were calculated using standard conversion factors [17]. The study was conducted in accordance with human experiments Helsinki Declaration (revised 2004) and approved by the Monash Health and RMIT University Human Research Ethics Committees. All participants in this study gave their written informed consent prior to data recording.

Recording methods

A digital tablet (Wacom Intuos Pro-Large) with an ink-pen having a pressure sensor was used for the experiments. The advantage of this device was that it gave participants the feeling of conventional pen and paper, likely to be less defamiliarizing to older subjects. Participants sat on a chair and the tablet was placed on an adjustable desk, the height and positioning of which was selected by each participant.

Customized software was developed to record and analyse data from the tablet. This registered the x–y coordinates, pen pressure and time stamp at a 133 Hz sampling rate.

Handwriting tasks

Handwriting specimens were obtained for six different tasks, which were selected such that there was an increase in the level of complexity and attention for each successive task.

1. Repeating the letter 'e'[8]
2. Repeating the letter 'b' then repeating the letter 'd'
3. Repeated writing of 'bd'
4. Repeatedly writing the word 'hello' [10]
5. Copying a sentence [18]
6. Written animals category fluency test [19]

The task of repeatedly writing of the letter e was assumed to be the most basic assessment of the fine motor skills of writing. Because writing strokes are differentially affected by PD, the letters 'b' and 'd' were chosen for Tasks 2 and 3 [9, 20]. Tasks 5 and 6 were more complex with increased levels of cognitive loading. Task 5 required attention and visuospatial memory whereas Task 6 involved working memory and searching for stored information [19]. Task 6 was administered as a written version of the category fluency test. Participants were asked to write up to 15 names of animals in a horizontal list without any time limit. Figure 1 shows sample images of all writing tasks performed by a PD participant.

Computation of kinematic features

The writing data for each task were segmented based on pen-up and pen-down motions. Segments of length less than 0.5 mm corresponded to dots and were excluded. Vertical and horizontal velocity and acceleration were calculated separately to understand the effect in each direction [21].

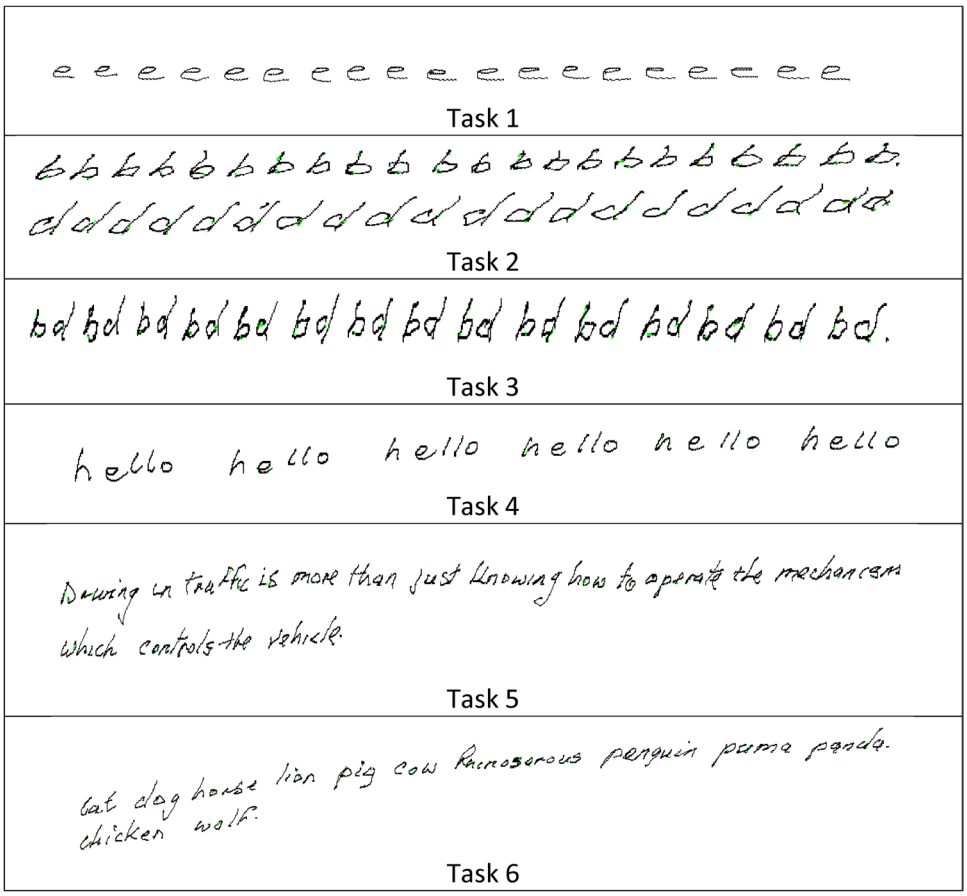

Fig. 1 Sample images of writing tasks performed by a PD participant in an off state

The kinematic features extracted from each segment were: (i) speed of pen tip while moving on the surface S, (ii) velocity in x direction v_x and y direction v_y and (iii) rate of change of velocity of the pen tip in x direction a_x and y direction a_y. Each segment was weighted according to the length of that segment to calculate weighted average kinematic features as previously described [7]. This ensured that small segments associated with pen-up motions did not unduly influence the results.

Statistical analysis

Continuous non-parametric features (by Shapiro–Wilk test) obtained from all the 6 tasks for On and Off state of PD groups were compared using the Wilcoxon signed rank test, and the Mann–Whitney *U* test for independent samples obtained from PD in on state and controls. Spearman rank-order correlation coefficients were calculated to assess the strength of associations between the kinematic features with UPDRS score for all the three groups [22]. The median values have been reported as the descriptive statistics for kinematic features. Effect sizes (*r*)were computed for the differences between the groups [23]. Data analysis was performed using IBM SPSS statistical software package.

Results

Table 1 contains demographic information and a summary of the motor and cognitive assessments for the participants. UPDRS-III scores decreased from 26.8 ± 9.50 in off states to 19.6 ± 8.62 when on. Four PD subjects and two controls scored below 26 on the MoCA. There was only a small difference in mean MoCA score between the groups (27.2 versus 28.0), of negligible clinical significance. All participants were fluent in English. None had major neurocognitive disability according to DSM-V criteria [24].

Table 2 shows the median values of five kinematic measures for each of the six handwriting tasks along with the Z statistic (Wilcoxon signed rank test) and *U* statistic (Mann–Whitney *U* test) results. Comparing PD off states with on states, most kinematic features in Task 1 showed highly significant ($p < 0.001$) improvement (Wilcoxon signed rank test for all on–off comparisons), with large effect size ($r > 0.5$) [23]. The differences between off and on for Task 3 were significant for all the features with $p < 0.01$ or $p < 0.05$ and moderate to large effect size. Horizontal acceleration for Task 2 and Task 4 did not respond significantly to levodopa. For Task 5 and Task 6, no significant difference was observed for any feature. Comparing PD patients in on

Table 1 Demographic and clinical information, PD patients and controls

	PD	Control group	p values
Number of subjects	24	25	
Age	71.6 ±7.14	69.7 ± 5.88	0.25[a]
Gender (male, female)	13, 11	14, 11	0.9[b]
Handedness (right, left)	20, 4	23, 2	0.42[b]
Highest educational level (secondary, tertiary)	18, 6	13, 12	0.14[b]
Disease duration, years	5 ± 2.88	–	
UPDRS-III ON [0-132]	19.6 ± 80.62	–	
UPDRS-III OFF [0–132]	26.80 ± 9.50	–	
UPDRS-III tremor sub-scores [0–40]	3.67 ± 4.62	–	
MoCA [0–30]	27.2 ± 2.63 (range 23–30)	280 ± 1.70 (range 24–30)	0.37[a]
Levodopa equivalent daily dosage (mg)	473 ± 292	–	

Values are mean ± SD, comparison between groups is performed using [a]independent *t* test and [b]Chi-square test 2-tailed

states with controls, all features showed a significant difference ($p < 0.01$ by Mann–Whitney U) for all of the tasks with moderate to large size effects. Figure 2 shows the median values of the speed of handwriting for all the handwriting activities in PD and control groups.

Spearman's rho did not reveal a significant correspondence in PD patients between UPDRS-III scores in off or *on* states and kinematic measures, or between the levodopa motor response (off minus on UPDRS-III score) and kinematic measures. There was no significant correspondence between aggregate tremor sub-score (UPDRS items 3.15–3.18) and kinematic measures.

Discussion

Our set of writing tests began with the simple letter repetition of Task 1 and introduced incremental complexity in motor planning at each stage up to Task 5, while both Tasks 5 and 6 required substantially greater cognitive resources. As shown in Table 2, there was a progressive reduction in the statistical significance of improvements from off to on for multiple kinematic parameters across the tasks. By Tasks 5 and 6, there were no significant differences between the *on* and off states. We conclude that levodopa improves the kinematics of basic penmanship (Tasks 1–4), but that much of this benefit was lost for sentence copying and written word fluency, where a substantial lexical semantic element had been added. Lewis et al. showed that PD patients with no cognitive impairment perform at a similar level to controls on Semantic fluency verbal test (animals) testing [25]. All six tasks can be considered to require similar levels of fine motor control. It is evident that levodopa improves this, which is in agreement with previous studies [8, 10], while the findings of lack of improvement due to levodopa in Tasks 5 and 6 cannot be attributed to the production of writing alone.

We have observed that the levodopa effect is incomplete. Differences between PD patients in *on* states and controls persist for almost all the writing tasks ($p < 0.01$). This confirms that computerised writing analysis appears to be a robust discriminator of PD dysgraphia from age-related changes in writing style [6, 26]. The scope of this paper is kinematics—the characteristics of motion. We did not examine static writing size. Nor did we consider temporal aspects of pen lifts within and between words, which may reflect time taken for motor planning in more complex writing tasks [27].

David Marsden, in developing his ideas about the role of the basal ganglia in motor planning, considered the act of writing [28]. He used examples of his own script to show that the character of penmanship is independent of the muscles used to execute it, revealing a common motor plan. Referring to observations previously made by Schwab et al. [29], he highlighted the breakdown in motor planning when PD patients perform simultaneous or sequential actions [28]. This dual-task phenomenon is relevant to our finding that there is little significant levodopa response when the PD patients are required to read and memorize while writing. It agrees with previous research which found that writing amplitude was decreased in PD patients but not controls when combined with a secondary task of counting high and low tones [12]. None of our patients had the cognitive disabilities that are often associated with advanced PD. Most had MoCA scores of greater than 26 and the group difference from controls was negligible, suggesting that the differences between the handwriting tasks are not cognitively

Table 2 Kinematic features for the six writing tasks

	Task 1		Task 2		Task 3		Task 4		Task 5		Task 6	
	Median	Effect Sizer	Median	Effect Sizer	Median	Effect Sizer	Median	Effect Sizer	Median	Effect Sizer	Median	Effect Sizer
Speed,s (mm/sec)												
Off	21.16		22.60		24.02		20.99		22.54		22.99	
On	26.18^{***}	0.59	26.38^{***}	0.50	26.13^{**}	0.35	27.94^{**}	0.36	25.04	0.24	22.95	0.25
Controls	48.28^{+++}	0.45	39.08^{+++}	0.48	39.07^{+++}	0.49	44.54^{+++}	0.53	38.71^{+++}	0.62	39.07^{+++}	0.60
Horizontal velocity, $\bar{v}_x$ (mm/sec)												
Off	16.43		11.05		11.03		12.78		13.18		13.00	
On	21.28^{***}	0.58	12.88^{*}	0.33	12.65^{*}	0.32	17.13^{*}	0.30	15.58	0.26	14.24	0.19
Controls	19.29^{++}	0.42	18.41^{++}	0.39	19.29^{++}	0.38	19.94^{+}	0.34	22.06^{+++}	0.51	24.22^{+++}	0.56
Vertical velocity, $\bar{v}_y$ (mm/sec)												
Off	9.58		15.03		17.45		15.93		15.47		14.07	
On	10.47^{***}	0.50	17.48^{***}	0.51	18.72^{*}	0.35	17.45^{*}	0.42	15.92	0.25	14.92	0.28
Controls	31.45^{++}	0.41	27.37^{+++}	0.45	31.45^{+++}	0.51	30.17^{+++}	0.54	26.01^{+++}	0.62	25.82^{+++}	0.55
Horizontal acceleration, a_x(mm/sec^2)												
Off	402.71		377.16		307.03		407.81		456.18		436.15	
On	679.60^{***}	0.55	413.44	0.27	435.43^{*}	0.30	528.41	0.24	558.38	0.23	526.61	0.18
Controls	682.4^{++}	0.43	643.96^{+++}	0.46	682.42^{+++}	0.41	686.37^{++}	0.39	811.99^{+++}	0.48	797.42^{+++}	0.55
Vertical acceleration, a_y (mm/sec^2)												
Off	237.37		488.00		561.41		563.10		543.76		482.18	
On	319.85^{***}	0.54	544.31^{***}	0.47	572.67^{*}	0.31	605.78^{*}	0.33	567.00	0.24	520.73	0.30
Controls	1046^{+++}	0.45	959^{+++}	0.51	1046^{+++}	0.56	1013^{+++}	0.56	945^{+++}	0.60	946^{+++}	0.56

Results appear as median. Significant differences between off and on states

$^{***}p \leq 0.001$, $^{**}p < 0.01$ *and* $^{*}p < 0.05$ by two tailed using Wilcoxon signed rank test. Comparison of PD patients in on states with controls: $+++p \leq 0.001$, $++p < 0.01$, $+P < 0.05$ two-tailed using Mann–Whitney *U* test for total samples $n=49$

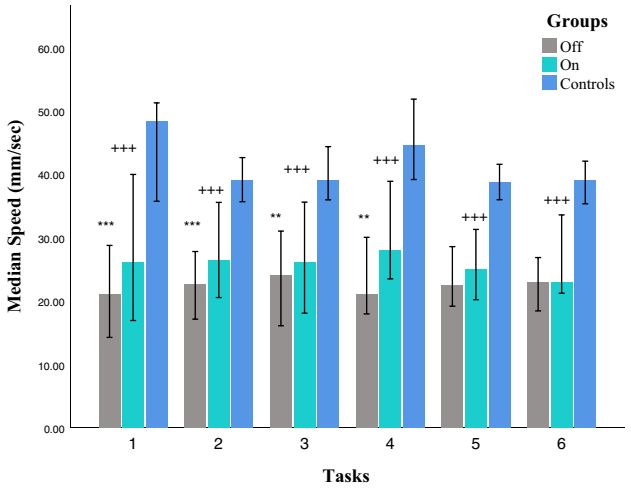

Fig. 2 Bar chart of median writing speeds of PD participants in on and off states, and controls

based. Rather, they are likely to reflect a deficit in the simultaneous automatic execution of learned motor plans, a hypothesis proposed by Redgrave et al. [30]. This supports the findings by Maillet et al. using functional MRI during unilateral hand movement, speech production and both. Cerebral activation was restricted with simultaneous movement in PD, and this dual-task effect was only partially improved by levodopa [31].

Speech and handwriting are complex activities that comprise multiple simultaneous motor plans. Both are modes for communication that engage the language and cognitive faculties. For both, there is a conflicting body of research about the extent and pattern of levodopa responsiveness in PD. The 'hypokinetic dysarthria' of PD consists of hypophonia and reduced variability in pitch and loudness, roughly analogous to limb bradykinesia. Previous acoustic analyses of phonation have shown substantial [32] or little [33] improvement after levodopa administration, though overall intelligibility does seem to respond [34]. The small study by Ho et al., which used rigorously defined *off* phase testing of drug response, found an improvement in the intensity and speed of speech that appeared to equate to an overall upscaling of movement [32]. But pitch and articulation were little changed, and intensity decay over a breath cycle worsened if anything. There are similarities here with our findings—that levodopa benefits primary motor activity but is less effective for simultaneous motor plans that contain cognitive input. It could be argued that freezing of gait, which shows variable levodopa responsiveness and sometimes appears resistant to the drug, demonstrates this inability to perform multiple tasks when a patient is distracted by an external stimuli [35].

Conclusion

This controlled study of patients in the early–middle stages of PD has explored task-dependent aspects of computerized kinematic handwriting analysis in relation to dopaminergic treatment. These techniques have shown promise as an early detector of parkinsonian motor deficits [6]. Our findings on dual-task effects suggest that a panel of writing tests for such research should include ones that require higher-level cognitive and language processing in addition to simpler letter production. This would increase the range of sensitivity as a potential biomarker in patients known to be at risk for developing PD. Thereafter, the weaker levodopa responsiveness of sentence copying and written word fluency would make these tests more stable indicators of motor progression once symptomatic treatment has been commenced.

Acknowledgements We acknowledge the funding supported by RMIT University scholarship and clinical support from Monash Medical Centre, Melbourne, Australia.

Compliance with ethical standards

Conflicts of Interest The authors declare that they have no conflict of interest.

References

1. Kinnier Wilson S (1925) The Croonian Lecutures on some disorders of mortility and of muscle tone, with special reference to the corpus striatum. Lancet ii:1–10
2. Shukla AW, Ounpraseuth S, Okun MS, Gray V, Schwankhaus J, Metzer WS (2012) Micrographia and related deficits in Parkinson's disease: a cross-sectional study. BMJ Open 2(3):e000628–e000628
3. Letanneux A, Danna J, Velay JL, Viallet F, Pinto S (2014) From micrographia to Parkinson's disease dysgraphia. Mov Disord 29(12):1467–1475. https://doi.org/10.1002/mds.25990
4. San Luciano M, Wang C, Ortega RA, Yu Q, Boschung S, Soto-Valencia J, Bressman SB, Lipton RB, Pullman S, Saunders-Pullman R (2016) Digitized spiral drawing: a possible biomarker for early Parkinson's disease. PloS One 11(10):e0162799
5. Pereira CR, Pereira DR, da Silva FA, Hook C, Weber SA, Pereira LA, Papa JP (2015) A step towards the automated diagnosis of Parkinson's disease: analyzing handwriting movements. In: 2015 IEEE 28th international symposium on computer-based medical systems. pp 171–176
6. Drotar P, Mekyska J, Rektorova I, Masarova L, Smekal Z, Faundez-Zanuy M (2015) Decision support framework for Parkinson's disease based on novel handwriting markers. IEEE Trans Neural Syst Rehabil Eng 23(3):508–516. https://doi.org/10.1109/TNSRE.2014.2359997
7. Zham PZ, Kumar DK, Dabnichki P, Arjunan S, Raghav S (2017) Distinguishing different stages of Parkinson's disease

using composite index of speed and pen-pressure of sketching a spiral. Front Neurol 8:435
8. Cobbah W, Fairhurst MC (2000) Computer analysis of handwriting dynamics during dopamimetic tests in Parkinson's disease. In: Euromicro Conference, 2000. Proceedings of the 26th IEEE, pp 414–418
9. Eichhorn T, Gasser T, Mai N, Marquardt C, Arnold G, Schwarz J, Oertel W (1996) Computational analysis of open loop handwriting movements in Parkinson's disease: a rapid method to detect dopamimetic effects. Mov Disord 11(3):289–297
10. Tucha O, Mecklinger L, Thome J, Reiter A, Alders G, Sartor H, Naumann M, Lange K (2006) Kinematic analysis of dopaminergic effects on skilled handwriting movements in Parkinson's disease. J Neural Transm 113(5):609–623
11. Poluha P, Teulings H-L, Brookshire R (1998) Handwriting and speech changes across the levodopa cycle in Parkinson's disease. Acta Psychol 100(1):71–84
12. Broeder S, Nackaerts E, Nieuwboer A, Smits-Engelsman BC, Swinnen SP, Heremans E (2014) The effects of dual tasking on handwriting in patients with Parkinson's disease. Neuroscience 263:193–202. https://doi.org/10.1016/j.neuroscience.2014.01.019
13. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55(3):181–184
14. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ (2010) Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain 133(6):1755–1762
15. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord 23(15):2129–2170
16. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53(4):695–699
17. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 25(15):2649–2653
18. Zham P, Arjunan S, Raghav S, Kumar DK (2017) Efficacy of guided spiral drawing in the classification of Parkinson's Disease. IEEE J Biomed Health Inform 22(5):1648–1652
19. Pfeiffer HCV, Løkkegaard A, Zoetmulder M, Friberg L, Werdelin L (2014) Cognitive impairment in early-stage non-demented Parkinson's disease patients. Acta Neurol Scand 129(5):307–318
20. Thomassen AJ, Teulings H-L (1983) Constancy in stationary and progressive handwriting. Acta Physiol (Oxf) 54(1–3):179–196
21. Ma H-I, Hwang W-J, Chang S-H, Wang T-Y (2013) Progressive micrographia shown in horizontal, but not vertical, writing in Parkinson's disease. Behav Neurol 27(2):169–174
22. du Prel J-B, Röhrig B, Hommel G, Blettner M (2010) Choosing statistical tests: part 12 of a series on evaluation of scientific publications. Dtsch Ärztebl Int 107(19):343
23. Fritz CO, Morris PE, Richler JJ (2012) Effect size estimates: current use, calculations, and interpretation. J Exp Psychol Gen 141(1):2
24. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Association, Arlington
25. Lewis FM, Lapointe LL, Murdoch BE, Chenery HJ (1998) Language impairment in Parkinson's disease. Aphasiology 12(3):193–206
26. Zham P, Arjunan S, Raghav S, Kumar DK (2017) Efficacy of guided spiral drawing in the classification of Parkinson's Disease. IEEE J Biomed Health Inform 22(5):1648–1652
27. Rosenblum S, Samuel M, Zlotnik S, Erikh I, Schlesinger I (2013) Handwriting as an objective tool for Parkinson's disease diagnosis. J Neurol 260(9):2357–2361
28. Marsden C (1982) The mysterious motor function of the basal ganglia: the Robert Wartenberg Lecture. Neurology 32(5):514–539
29. Schwab RS, England AC, Peterson E (1959) Akinesia in Parkinson's disease. Neurology 9(1):65–65
30. Redgrave P, Rodriguez M, Smith Y, Rodriguez-Oroz MC, Lehericy S, Bergman H, Agid Y, DeLong MR, Obeso JA (2010) Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. Nat Rev Neurosci 11(11):760
31. Maillet A, Krainik A, Debû B, Troprès I, Lagrange C, Thobois S, Pollak P, Pinto S (2012) Levodopa effects on hand and speech movements in patients with Parkinson's disease: a FMRI study. PLoS One 7(10):e46541
32. Ho AK, Iansek R, Marigliani C, Bradshaw JL, Gates S (1999) Speech impairment in a large sample of patients with Parkinson's disease. Behav Neurol 11(3):131–137
33. Rusz J, Čmejla R, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E (2011) Acoustic assessment of voice and speech disorders in Parkinson's disease through quick vocal test. Mov Disord 26(10):1951–1952
34. De Letter M, Santens P, Van Borsel J (2005) The effects of levodopa on word intelligibility in Parkinson's disease. J Commun Disord 38(3):187–196
35. Ricciardi L, Bloem BR, Snijders AH, Daniele A, Quaranta D, Bentivoglio AR, Fasano A (2014) Freezing of gait in Parkinson's disease: the paradoxical interplay between gait and cognition. Parkinsonism Relat Disord 20(8):824–829