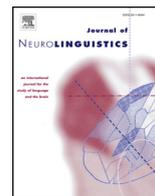




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Short communication

Levodopa effect on spontaneous speech in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is associated with verb deficits detected with tasks including picture naming and verbal fluency. However, these deficits are not frequently reported by the patients themselves. Levodopa, the gold standard for motor symptoms in PD, has been previously implicated to improve these verb deficits. We evaluated the effect of levodopa by using a spontaneous speech task which is more naturalistic than the previously used tasks to detect verb deficits. Thirty PD patients, and 30 age-, gender-, years of education-matched healthy controls were included. Patients were tested while motor 'on' and 'off'. Levodopa did not affect spontaneous speech, although it improved the motor symptoms. Compared to controls, PD patients produced shorter and a lower number of sentences. The verb deficit was independent of cognitive or motor performance. The pathophysiology of motor symptoms and verb deficits most likely differ, and levodopa does not improve verb deficits during spontaneous speech.

1. Introduction

Parkinson's disease (PD) is associated with verb deficits whereas noun processing is preserved (Cardona et al., 2013). Comparing action and non-action verbs, Herrera and colleagues have shown that although PD patients have an overall verb deficit compared to healthy controls, the verb deficit is more pronounced for action verbs (Herrera, Rodríguez-Ferreiro, & Cuetos, 2012). Levodopa, the gold standard for PD motor symptoms (Poewe, Antonini, Zijlmans, Burkhard, & Vingerhoets, 2010), has been suggested to improve these verb deficits (Herrera & Cuetos, 2012; Herrera, Cuetos, & Ribacoba, 2012a). However, verb deficits are associated with frontotemporal regions and do not directly correlate with motor symptoms (Péran et al., 2003). Thus, verb deficits likely stem from disruption in different basal ganglia circuits rather than the motor circuit.

Although the verb deficit has been captured by various tasks including picture naming, verbal fluency and word generation (Bayram & Akbostanci, 2018), PD patients do not commonly report a verb deficit. Considering how most of the tasks previously used to study the verb deficit in PD consist of tasks requiring production of words from certain categories (noun or verb), without introducing planning for sentence structures, we aimed to evaluate the verb deficit using a more naturalistic task to reflect daily speaking. Thus we used a spontaneous speech task, which allows production of nouns and verbs as preferred. We also briefly evaluated whether changes in verb or noun production are associated with cognitive or motor changes induced by levodopa.

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2. Material and methods

Thirty PD patients diagnosed with idiopathic PD based on Queen Square Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992) and 30 healthy controls (HC) matched for age, gender, years of education and handedness were recruited. As MMSE was shown to be a better screening tool than MoCA in Turkish PD patients (Ozdilek & Kenangil, 2014), MMSE was used to determine cognitive impairment. Patients with a score below 24 (Güngen, Ertan, Eker, Yaşar, & Engin, 2002) were excluded based on the criteria for mild cognitive impairment and dementia in PD (Emre et al., 2007; Litvan et al., 2012). Patients with any other neurologic or psychiatric disorders affecting speech production were excluded based on the neurological exam. All participants were native Turkish speakers, and signed written informed consents prior to participation. The study was approved by the local ethics committee and conducted in accordance with Declaration of Helsinki.

The Unified Parkinson's Disease Rating Scale (UPDRS)-Part III was used for motor impairment in PD. The Montreal Cognitive Assessment (MoCA) was used to examine cognition. The rationale behind using the MoCA instead of MMSE was due to MoCA's inclusion of more cognitive domains than MMSE (Nasreddine et al., 2005). Spontaneous speech was evaluated using Cookie Theft Picture. Participants were asked to explain the picture without any word or time limits. Healthy controls were tested only once, while PD patients were tested twice: during motor 'on' (45 min after levodopa dose, optimal motor response) and 'off' (> 12 h after the last dose). Half of the PD patients were randomly assigned to be first tested during 'off' and the other half during 'on', to minimize the confounding practice effects.

The examiner rating the scales and tests was blinded to the motor states of the patients. Outcome measures of spontaneous speech included; the number of utterances, words, verbs and nouns; mean length of utterance (MLU), verb and noun variances. For the calculation of MLU; the number of words were divided by the number of utterances. Verb and noun variances corresponded to the number of different verbs and nouns.

2.1. Statistical analyses

Statistics were done using IBM SPSS 25.0 (Armonk, NY). Variables are reported as mean (standard deviation) or percentage. PD and HC group comparisons were done using Chi-squared and independent samples *t* tests. Levodopa effect within the PD group was evaluated using paired samples *t*-test. The associations between cognition, motor symptoms and spontaneous speech were evaluated using Pearson's correlation coefficients. $p < .05$ was considered statistically significant.

3. Results

Mean age was 56.70 (8.25) in HC and 61.28 (9.72) in the PD group. Mean years of education was 10.47 (3.99) in HC and 8.71 (4.09) in the PD group. 40% of HC, and 33.3% of PD were female. 93.3% of HC, and 90% of PD were right-handed. In the PD group; disease duration was 8.14 (7.46) years and levodopa equivalent daily dose (LEDD) was 961.45 (365.236) milligrams. 53.3% of the PD patients had left-side onset.

Cognition and spontaneous speech scores of the groups are shown in Fig. 1. MoCA scores of the PD patients during both 'off' and 'on' were similar compared to HC ($p = .924$ for 'off' vs HC, $p = .426$ for 'on' vs HC). Within the PD group, levodopa did not significantly affect MoCA ($p = .308$); but reduced the UPDRS-Part III scores (23.50 (9.25) while 'off' vs 16.27 (8.95) while 'on', $p < .001$).

Compared to HC; MLU, word, verb, noun counts and verb variance was lower in the PD motor 'off' ($p = .002$, $p = .009$, $p < .001$, $p = .013$, $p = .006$; respectively). No difference was found in utterance count and noun variance between HC and PD motor 'off' ($p = .106$, $p = .151$; respectively). Compared to HC; MLU, word, verb count and verb variance was lower in the PD motor 'on' ($p < .001$, $p = .030$, $p = .008$, $p = .022$; respectively). No difference was found in utterance, noun count and noun variance between HC and PD motor 'on' ($p = .659$, $p = .143$, $p = .424$; respectively). Pairwise comparisons within the PD group showed that none of the outcome measures were significantly affected by levodopa ($p > .05$ for all).

There were no significant correlations between the spontaneous speech measures and MoCA in HC ($p > .05$ for all). MoCA was positively correlated with noun count ($r = 0.424$, $p = .022$) and noun variance ($r = 0.487$, $p = .007$) in the PD motor 'off'. No other correlations were found between the spontaneous speech measures and MoCA or UPDRS-Part III during 'off' or 'on' in the PD group ($p > .05$ for all).

4. Discussion

Our findings indicate that PD patients produced shorter sentences and shorter descriptions overall. PD patients had a verb deficit independent of cognitive or motor performance. Levodopa did not affect spontaneous speech. Lack of difference between MoCA scores during 'on' and 'off' in PD suggest that levodopa did not have immediate cognitive effects, although it significantly improved the motor symptoms in these patients. The lack of correlation between motor performance and language or cognitive abilities are also supported by subthalamic nucleus deep brain stimulation studies. Whereas motor symptoms are significantly improved by this approach, decline in verbal fluency is one of the most commonly reported cognitive effects of the surgery (Højlund, Petersen, Sridharan, & Østergaard, 2017). Imaging studies have shown that basal ganglia-thalamocortical network involving dorsolateral prefrontal cortex and inferior frontal gyrus are associated with the verbal fluency changes in PD (Kalbe et al., 2009; Schroeder et al., 2003). Thus, the language deficits in PD do not appear to be directly associated with the motor network.

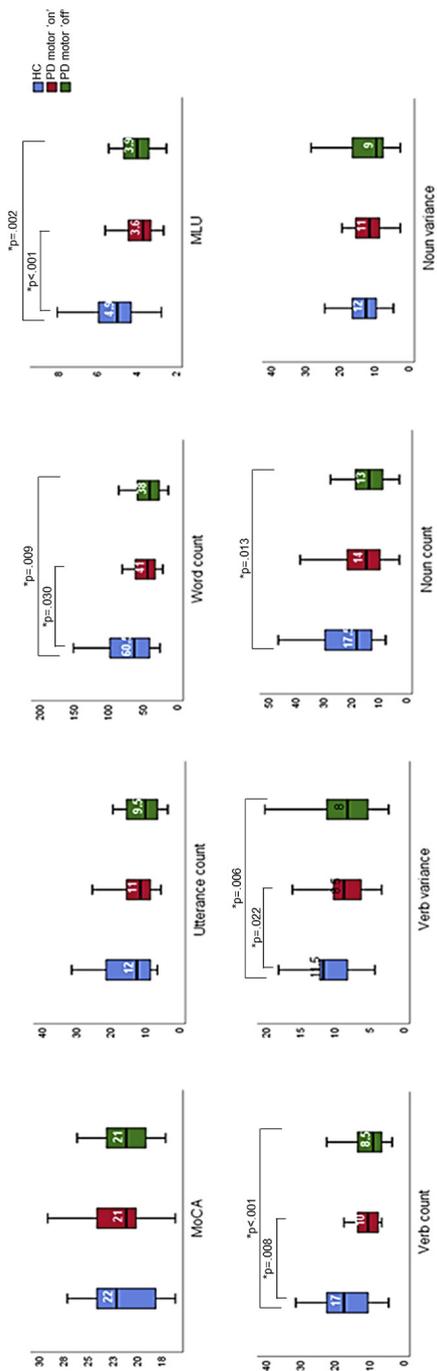


Fig. 1. MoCA and spontaneous speech outcome measures in HC and PD while motor 'on' and 'off'. Significant differences between groups are marked with *.

Our results support previous findings on verb impairment in PD (Herrera & Cueto, 2012; Herrera, Cueto, & Ribacoba, 2012b; Péran et al., 2003). However, the language deficit does not appear to be limited with verbs, as patients provided less and shorter sentences as well. Different speech tasks can lead to different results as internal planning burden differs between the tasks (Kempler & Lancker, 2002). While repetition and reading tasks require externally provided models, recited speech uses memorized internal models. On the other hand, conversational speech relies on newly produced internal models (Van Lancker Sidtis, Cameron, & Sidtis, 2012). Aphasia studies have suggested that single-word tasks like naming, and conversational speech tasks do not always reveal the same results (Mayer & Murray, 2003). Thus, the use of more naturalistic tasks such as a spontaneous speech task may reflect daily linguistic deficits better than single word production tasks. The overall brevity of speech produced by the PD patients may be the reason why these patients do not report a verb deficit in particular. Language deficit in PD appears to extend beyond verbs.

There were no correlations between cognition and verb production. However, the use of a brief scale for cognition significantly limits our ability to evaluate the associations between cognition and spontaneous speech in detail. Executive function, for instance, has been previously shown to correlate with verb production (Crescentini, Mondolo, Biasutti, & Shallice, 2008) whereas Bocanegra and colleagues did not find any significant correlations between executive functions and verbs (Bocanegra et al., 2015). Other factors commonly observed in PD, but not evaluated in our study such as depression, anxiety, apathy and motor speech disturbances may also have led to this speech pattern, and should be assessed in future studies.

As the PD patients were tested with MoCA and the spontaneous speech task twice in such a short interval, the practice effects were inevitable. Although we tested half of the patients first during 'off' and the other half vice versa; we were not able to exclude the possible interaction effects of levodopa and practice effects. Introduction of a test first during motor 'on' may be associated with increased priming compared to first performing during motor 'off'. This interaction effect could be studied further in future studies.

Overall, levodopa does not have beneficial effects on spontaneous speech. Future studies, including neuroimaging and other contributing non-motor symptoms, may determine the pathophysiology of verb deficits in PD.

Declarations of interest

Ece Bayram: None.

Eda Aslanbaba: None.

Muhittin Cenk Akbostanci: Honoraria from Abbott, Abdi Ibrahim, Allergan, Bohringer Ingelheim, Gen Ilac, Generica, Glaxo Smith Kline, Medtronic, Lundbeck, Novartis, Ilko and SantaFarma.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jneuroling.2019.03.001>.

References

- Bayram, E., & Akbostanci, M. C. (2018). Neural foundations of action-related language: Studies in Parkinson's disease. *Turkish Journal Of Neurology*, 2018(1), 3–12. <https://doi.org/10.4274/tnd.04796>.
- Bocanegra, Y., García, A. M., Pineda, D., Buriticá, O., Villegas, A., Lopera, F., ... Ibáñez, A. (2015). Syntax, action verbs, action semantics, and object semantics in Parkinson's disease: Dissociability, progression, and executive influences. *Cortex*, 69, 237–254. <https://doi.org/10.1016/j.cortex.2015.05.022>.
- Cardona, J. F., Gershanik, O., Gelormini-Lezama, C., Houck, A. L., Cardona, S., Kargieman, L., ... Ibáñez, A. (2013). Action-verb processing in Parkinson's disease: New pathways for motor-language coupling. *Brain Structure and Function*. <https://doi.org/10.1007/s00429-013-0510-1>.
- Crescentini, C., Mondolo, F., Biasutti, E., & Shallice, T. (2008). Supervisory and routine processes in noun and verb generation in nondemented patients with Parkinson's disease. *Neuropsychologia*, 46(2), 434–447. <https://doi.org/10.1016/j.neuropsychologia.2007.08.021>.
- Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., ... Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders*. <https://doi.org/10.1002/mds.21507>.
- Güngen, C., Ertan, T., Eker, E., Yaşar, R., & Engin, F. (2002 Winter). Reliability and validity of the standardized Mini Mental State Examination in the diagnosis of mild dementia in Turkish population. *Türk Psikiyatri Dergisi*, 13(4), 273–281.
- Herrera, E., & Cueto, F. (2012). Action naming in Parkinson's disease patients on/off dopamine. *Neuroscience Letters*, 513(2), 219–222. <https://doi.org/10.1016/j.neulet.2012.02.045>.
- Herrera, E., Cueto, F., & Ribacoba, R. (2012a). Verbal fluency in Parkinson's disease patients on/off dopamine medication. *Neuropsychologia*, 50(14), 3636–3640. <https://doi.org/10.1016/j.neuropsychologia.2012.09.016>.
- Herrera, E., Cueto, F., & Ribacoba, R. (2012b). Verbal fluency in Parkinson's disease patients on/off dopamine medication. *Neuropsychologia*, 50(14), 3636–3640. <https://doi.org/10.1016/j.neuropsychologia.2012.09.016>.
- Herrera, E., Rodríguez-Ferreiro, J., & Cueto, F. (2012). The effect of motion content in action naming by Parkinson's disease patients. *Cortex*, 48(7), 900–904. <https://doi.org/10.1016/j.cortex.2010.12.007>.
- Højlund, A., Petersen, M. V., Sridharan, K. S., & Østergaard, K. (2017). Worsening of verbal fluency after deep brain stimulation in Parkinson's disease: A focused review. *Computational and Structural Biotechnology Journal*, 15, 68–74. <https://doi.org/10.1016/j.csbj.2016.11.003>.
- Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *Journal of Neurology Neurosurgery and Psychiatry*. <https://doi.org/10.1136/jnnp.55.3.181>.
- Kalbe, E., Voges, J., Weber, T., Haarer, M., Baudrexel, S., Klein, J. C., ... Hilker, R. (2009). Frontal FDG-PET activity correlates with cognitive outcome after STN-DBS in

- Parkinson disease. *Neurology*, 72(1), 42–49. <https://doi.org/10.1212/01.wnl.0000338536.31388.f0>.
- Kempler, D., & Lancker, D. Van (2002). Effect of speech task on intelligibility in dysarthria: A case study of Parkinson's disease. *Brain and Language*. <https://doi.org/10.1006/brln.2001.2602>.
- Litvan, I., Goldman, J. G., Tröster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., ... Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Movement Disorders*, 27(3), 349–356. <https://doi.org/10.1002/mds.24893>.
- Mayer, J. F., & Murray, L. L. (2003). Functional measures of naming in aphasia: Word retrieval in confrontation naming versus connected speech. *Aphasiology*. <https://doi.org/10.1080/02687030344000148>.
- Nasreddine, Z. S., Phillips, N. A., Bä@dirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... Chertkow, H. (2005). The montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, 53(4), 695–699. <https://doi.org/10.1111/j.1532-5415.2005.53221.x>.
- Ozdilek, B., & Kenangil, G. (2014). Validation of the Turkish version of the montreal cognitive assessment scale (MoCA-TR) in patients with Parkinson's disease. *The Clinical Neuropsychologist*, 28(2), 333–343. <https://doi.org/10.1080/13854046.2014.881554>.
- Péran, P., Rascol, O., Démonet, J. F., Celsis, P., Nespoulous, J. L., Dubois, B., et al. (2003). Deficit of verb generation in nondemented patients with Parkinson's disease. *Movement Disorders*. <https://doi.org/10.1002/mds.10306>.
- Poewe, W., Antonini, A., Zijlmans, J. C., Burkhard, P. R., & Vingerhoets, F. (2010). Levodopa in the treatment of Parkinson's disease: An old drug still going strong. *Clinical Interventions in Aging*, 5, 229–238. <http://www.ncbi.nlm.nih.gov/pubmed/20852670>.
- Schroeder, U., Kuehler, A., Lange, K. W., Haslinger, B., Tronnier, V. M., Krause, M., ... Ceballos-Baumann, A. O. (2003). Subthalamic nucleus stimulation affects a frontotemporal network: A pet study. *Annals of Neurology*, 54(4), 445–450. <https://doi.org/10.1002/ana.10683>.
- Van Lancker Sidtis, D., Cameron, K., & Sidtis, J. J. (2012). Dramatic effects of speech task on motor and linguistic planning in severely dysfluent parkinsonian speech. *Clinical Linguistics and Phonetics*, 26(8), 695–711. <https://doi.org/10.3109/02699206.2012.696307>.