Short Communication

Steadiness of syllable repetition in early motor stages of Parkinson’s disease

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** Abstract**

Patients with Parkinson’s disease (PD) show characteristic abnormalities in the performance of simple repetitive movements which can also be observed concerning speech rate and rhythm. The aim of the current study was to survey if patients with early PD already feature impairments of steady vocal pace performance based upon a simple syllable repetition paradigm. N = 50 patients with PD with mild to moderate motor impairment and n = 32 age-matched healthy controls were tested. Participants had to repeat a single syllable or a pair of alternating syllables in a self chosen steady pace or in a given pace of 80/min. The coefficient of variance was taken as measure of stability of repetition. As main and novel result, vocal pace performance was observed to be irregular in all patients, even in the subgroup of PD patients with only very mild motor impairment (Hoehn&Yahr stage 1), although the capacity of rapid syllable repetition was preserved. Weak correlations were found between the maximum repetition rate (but not with steadiness of repetition) and some distinctive Parkinsonian motor features as speech impairment and gait.

Assumed that subsequent studies are able to confirm these preliminary results, analysis of steadiness of syllable repetition might be a promising non-invasive tool for detection of subtle abnormalities of motor speech performance even in the early motor stages of PD.

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1. Introduction

Parkinson’s disease (PD) is a chronic progressive neurodegenerative neurological disease with a variety of motor and non-motor symptoms. According to the prevailing concept of the Braak stages, Lewy bodies as the neuropathological hallmarks of neurodegeneration in PD can initially be found in the olfactory bulb and lower brain stem nuclei years before the involvement of the dopamine producing cells in the substantia nigra pars compacta [1]. In these “premotor” stages a subtle acquisition of the patient’s medical history might reveal early symptoms as hypomnesia, constipation or REM sleep behavior disturbance and mood disorders [2], however, these symptoms are unspecific and not always present.

Furthermore, they occur in an otherwise “neurologically healthy” population and systematic collection of these symptoms is difficult, although attempts to meet this goal are actually underway [e.g. 3]. But, at present, the clinical diagnosis of PD still depends on the identification of a combination of the cardinal motor features of bradykinesia, rest tremor and rigidity. The diagnosis can be assured by a favorable response to dopaminergic medication and additional clinical signs as asymmetry of motor symptoms [4]. However, despite these criteria, the diagnosis of PD in its “early motor” stages is still challenging and often inaccurate [5]. Nonetheless, the first motor signs of PD which could allow a clinical diagnosis based upon accepted criteria do not occur until a substantial number of dopaminergic midbrain neurons are already degenerated [6]. And even in these early motor stages of PD, the clinical signs are often subtle and inconclusive leading to a delay of the diagnosis and of the initiation of treatment [7].

On the other hand, early diagnosis of PD is desirable to provide appropriate information and management of patients, the more so, as some studies suggest that early treatment may lead to a better outcome [8,9], although real neuroprotective or disease modifying therapeutic strategies are still not available. Therefore, there is an urgent need for the establishment of meaningful and easily applicable clinical tests to facilitate an early diagnosis of PD.
However, first motor symptoms of PD as slightly reduced arm-swing while walking or mild deterioration of dexterity are often unpecific, especially in elderly persons with co-existing morbidity, and therefore often enough do not suffice to establish the diagnosis of PD based upon conventional clinical/neurological examination. Accordingly, easy applicable tests with high sensitivity would be helpful to gain more diagnostic certainty already in the stages with subtle motor symptoms.

Abnormalities of the steady performance of simple repetitive “automated” movements are well-known features of PD and can be identified in different motor modalities as hand and finger movements, gait and also in Parkinsonian hypokinetic dysarthrias. This characteristic pattern of “motor instability” throughout the performance is thought to be induced by the complex dysfunction of planning, preparing, scaling and maintaining a once chosen simple motor program as a consequence of the underlying basal ganglia dysfunction [10]. Since speech can be subdivided down to the level of single utterances, one might expect abnormalities of vocal pace performance already on the level of very basic non-speech articulatory gestures. Indeed, in previous studies, our group had been able to show that patients in different stages of PD featured marked difficulties to steadily repeat a single syllable without changing the speed of the repetition [11,12]. However, the majority of these tested patients was in their rather moderate to advanced stages of PD and was affected by considerable co-existing voice and speech impairment as well. Up till now, it has not been investigated, if these abnormalities of steady vocal pace performance are already detectable in the very early motor stages of PD and if they occur somewhat independent from overall dysarthria.

2. Methods

N = 50 patients with PD (30 male) with mild to moderate motor impairment and n = 32 age-matched healthy controls (19 male) were tested. A group of n = 20 patients and n = 16 control speakers had already participated in a previous study of our group [12]. In the patients’ group Hoehn&Yahr/H&Y stages ([13] see Table 1) ranged from 1.0 to 2.2 (average H&Y 1.70, standard deviation 0.39) and the average Unified Parkinson’s Disease Motor Score/UPDRS III was 14.90 pts. (SD 6.08). Moreover, the axial symptoms of the UPDRS III except item 18/speech were calculated separately (items 19 [facial expression], 20 [head tremor], 21 [neck rigidity], 27 [arising from chair], 28 [posture], 29 [gait] and 30 [postural stability]) and related to the entire UPDRS Motor Score (axial ratio = axial subscore/overall UPDRS III).

Participants’ characteristics are listed in Table 2. At the time of examination, all patients were under stable but uncontrolled regime of dopaminergic medication for at least four weeks. Speech and motor examinations were performed 60–90 min after the morning dose of medication to ensure the “on”-state.

Speech samples were digitally recorded and anonymized by a study nurse using a commercial audio software and a head-set microphone. The speech task consisted of four subtests which have been described in detail in one previous study of our group [12]. Vowel keeping time/VKT (in milliseconds): Participants had to produce the German vowel/a/as long as possible with one single breath. Test 0: Participants had to reiterate the syllables /pa/ and /pa-ti/ as fast as possible for at least 5 s for the description of maximum syllable repetition rate (maxSylRep in syllables per second). Test 1: Repetition of the syllable /pa/ in a self chosen steady (isochronous) pace without acceleration or slowing articulatory velocity.

A subgroup of n = 32 patients with PD (20 male) and the entire control group performed two additional syllable repetition tasks (The results of this subgroup have already been presented on the MAVEBA conference 2013): Test 2: Repetition of the syllable /pa/ in a velocity of 80/min given by a metronome; participants had to listen to the pace first, then start with the syllable repetition; the metronome was stopped after four utterances, and participants had to keep the given pace. Test 3: Alternating repetition of the syllables /pa/ and /ti/ with the given metronome-based velocity of 80/min.

Each subtest was performed twice; the average values of first and second cycle were taken for the definite analyses. In each test the participants were asked to repeat the syllables at least 40 times (see Fig. 1). Only the first 30 utterances were taken for the definite analyses in order to avoid a modification of participants’ articulatory velocity by the expectance of the imminent end of the task. Based upon the oscillographic sound pressure signal of the recorded audio material, the period from onset of one vocalization until the following vocalization was defined as “interval”; interval duration (IntDur) was measured manually in milliseconds (ms). Stability of pace of the utterances was defined as relative coefficient of variation (COVS,SD) calculated for the intervals 5–30 in relation to the average interval length of the first 4 utterances (avIntDur1–4) following the formula: COVS,SD = SD1–30/[avIntDur1–4]/√26 × 100. Additionally, the average interval length of the intervals 5–17 and of the intervals 18–30 were related to the reference interval (avIntDur1–4); the difference of both average interval lengths (of the first and second half of the performance) in relation to the reference interval duration was defined as comprehensive measure of pace acceleration in the course of the repetition (%PA) with values greater than 0 indicating an acceleration. Furthermore, in test 3 (alternating repetition of a pair of syllables in a given pace), the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>definition of Hoehn&amp;Yahr stages [13].</th>
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<tbody>
<tr>
<td>Stage 0</td>
<td>No motor signs</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Symptoms on one body side only (purely unilateral motor signs)</td>
</tr>
<tr>
<td>Stage 1.5</td>
<td>Symptoms unilateral and also involving the neck and spine</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Symptoms on both sides (bilateral) but no impairment of balance</td>
</tr>
<tr>
<td>Stage 2.5</td>
<td>Mild bilateral symptoms with recovery when the ‘pull’ test is given (the doctor stands behind the person and asks them to maintain their balance when pulled backwards)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Balance impairment. Mild to moderate disease. Physically independent</td>
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<tr>
<td>Stage 4</td>
<td>Severe disability, but still able to walk or stand unsupervised</td>
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</table>

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<thead>
<tr>
<th>Table 2</th>
<th>Participants’ characteristics definition.</th>
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<tbody>
<tr>
<td></td>
<td>Entire PD group n = 50, 30 m Mean/SD/range</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.98/9.11/40–82</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>3.54/2.12/1–9</td>
</tr>
<tr>
<td>Hoehn&amp;Yahr</td>
<td>1.70/0.39/1–2</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>14.90/0.08/5–25</td>
</tr>
<tr>
<td>Axial UPDRS score</td>
<td>5.14/2.57/1–17</td>
</tr>
<tr>
<td>Axial ratio</td>
<td>0.39/0.19/0.08–0.85</td>
</tr>
<tr>
<td>UPDRS speech item</td>
<td>0.82/0.66/0–3</td>
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average interval duration of the first syllable /pa/ was related to the average interval duration of the second syllable /ti/ ("pa–ti ratio").

The acoustic analyses were performed by the author who initially was blinded to participants’ condition; in the subgroup of speakers who were analyzed before as part of previously published studies, inter-rater reliability was very high ($r = 0.984, p < 0.0001$).

Winstat\textsuperscript{5} was used for statistical analyses. T-test for independent groups was performed, since the variables were normally distributed (Shapiro–Wilk test). The adjusted level of significance was set at $p = 0.005$. Pearson correlation was used to test for significant correlations.

### 3. Results

Patients with PD showed significant aberrations of the steadiness of pace throughout the performance of different syllable repetition tasks (Table 3). COV in the PD group was elevated in the tasks consisting of a single syllable repetition in self-chosen pace and in the task with repetition of single syllables in a given pace as well, although only performed in a subgroup of $n = 32$ patients. In this subgroup, a further deterioration of steadiness of pace was observed in the task 3 with repetition of alternating syllables in a given pace, however, the differences were without statistical significance (paired $t$-test). Furthermore, the pa–ti ratio was significantly reduced in this PD group indicating that PD speakers connected the syllables /pa/ and /ti/ at the expense of keeping the steady pace.

In a subgroup of $n = 9$ patients with H&Y stage 1 (strictly unilateral symptoms), there was a significantly worse performance of syllable repetition (test 1) than in the control group ($COV_{test1} = 1.33 ± 0.38$ vs. $1.00 ± 0.28, p = 0.008$), although VKT was similar and maxSylRep was even higher in these patients $(5.23 ± 0.44$ vs. $3.72 ± 1.33, p = 0.002$). The results in the different H&Y groups are displayed in Fig. 2.

No significant differences were seen concerning the VKT as a simple measure of speech breathing and phonatory capacity. Furthermore, the maxSylRep was similar in the control and the entire PD group, even with a tendency to faster maximum repetition velocity, probably due to the patients with lower H&Y stages who featured faster performance (see above). Although there was a tendency of acceleration of pace in the task with syllable repetition in self-chosen velocity (test 1) indicated by slightly higher values for %PA, this difference was not significant ($p = 0.186$).

Weak correlations were seen between maxSylRep and the axial UPDRS ratio ($R = -0.318, p = 0.012$), the UPDRS speech item ($R = -0.279, p = 0.025$) and H&Y stage ($R = -0.274, p = 0.024$). No correlations were found between the other measures of vocal pace performance (COV, avIntDur, pa–ti ratio) and patients’ characteristics.

### 4. Discussion

According to the current data, impairment of steady vocal pace performance can be already detected in the early motor stages of PD although the abnormalities are less pronounced than in previous investigations of our group performed in a mixed group of patients with a much higher disease duration and overall motor disability [11,12]. Interestingly, in the current study, performance of syllable repetition was similar in all three tests and did not significantly worsen with higher complexity (keeping a given pace, alternating syllables) which we had previously found and interpreted as a hint for disturbed executive function [12]. Furthermore, the PD speakers showed a tendency to pace acceleration in the course of the performance, indicated by higher values for %PA, but this – in contrast to previous investigations of our group [14] – this difference was not significant in comparison to the control group. Maybe these discrepancies can be explained by the fact that in the current study, we did not stratify the PD group according to the more affected body side while acceleration of syllable repetition had been found to be more pronounced in patients with left-side dominant motor symptoms [15].

The abnormalities of steadiness of syllable repetition cannot be solely explained by alterations of phonatory capacity or articulatory deficits since vowel keeping time and also the maximum...
syllable repetition rate were similar in healthy speakers and PD patients with a tendency to perform even faster than the controls in patients with less severe motor impairment (indicated by a negative correlation between maxSylRep and H&Y stage). However, COV of test1 (steadily repeating a single syllable in a self-chosen pace) was found to be already significantly impaired in the small group of N = 9 patients with H&Y stage 1 as an indication that subtle abnormalities of vocal pace performance are present already in the earliest motor stages of PD, which had not been reported so far.

But, all patients had previously been diagnosed to suffer from PD according to established clinical criteria, and therefore, our findings cannot answer the question, if abnormal vocal pace performance is already present in the “gray area” of very early motor PD when accepted clinical criteria are often not yet applicable for the diagnosis of PD. Therefore, the current database is still too sparse to predict if measurement of syllable repetition could be a helpful tool for the very early diagnosis of PD or even predict its “full” development already in a stage of clinical uncertainty. Nevertheless, the present data seem to corroborate the hypothesis of a disruption of basic motor speech performance caused by dysfunctional basal ganglia networks with instability of basic motor programs which normally run in quasi automated mode which are detectable already in very early motor stages of the disease.

Although there were some correlations between H&Y stage and the axial UPDRS subscore (which includes the items which define the H&Y stages, as gait and balance) on the one hand and maxSylRep on the other, no such correlations were observed with steadiness of syllable repetition/COV which seem to indicate that pure velocity of repetition and steadiness are two different domains of basic motor speech performance, maybe also with independent pathophysiology.

In general, the pathophysiology of voice and speech impairment in PD and especially the aspect of dopaminergic influence is a matter of debate since findings concerning the effects of dopaminergic treatment on Parkinsonian dysthria are somewhat conflicting. In a simplifying subsumption, dopaminergic medication seems to have some beneficial effects on speech performance at least in a subgroup of patients, especially in the early stage of disease [16], whereas in the more advanced stages, dysthria seems to become unresponsive to dopaminergic treatment [e.g. 17,18]. Furthermore, the different aspects of voice and speech performance seem to respond differentially to dopaminergic treatment, since voice quality, pitch and intensity variability and some aspects of articulation have been found to improve, whereas aspects of speech rate, pause ratio and rhythmicity rather seem to be independent from dopaminergic stimulation [e.g. 16,19]. In the course of disease progression, overall speech performance tends to deteriorate without clear correlations to overall motor function, but with some correlations to some distinctive non-dopaminergic symptoms of the more advanced stages of PD as gait impairment and balance problems; therefore, dysthria has often been interpreted as an axial PD symptom [20,21]. Admittedly, the current investigation can shed no light on the question of dopaminergic responsiveness of the tested speech functions since all our patients were under different and uncontrolled regimen of dopaminergic medication. On the other hand, in a previous investigation of our group, impairment of steady syllable repetition had found to be unresponsive at least to short-time levodopa administration [22].

Although one has to carefully keep in mind that the simple syllable repetition paradigms used in the current study must not be equalized with “speech” as a complex means of conversation, it seems to be nonetheless justified to hypothesize that even highly complex speech tasks as monolog or conversation rely upon the integrity of very basic motor speech programs which have been shown to be dysfunctional in this present study. However, the pathophysiological mechanisms of these abnormalities have still not been sufficiently understood.

According to functional magnetic resonance imaging (fMRI) studies in healthy speakers, the production of monosyllabic utterances (as performed in the current study) was found to go along with activation of cortical areas in combination with basal ganglia and the cerebellum which facilitates rapid and coordinated movements required for consonant production [e.g. 23,24]. For speech tasks of higher complexity, for example, the production of disyllabic utterances (as performed in test 3 of the present study), the entire basic speech network has been shown to increase activity with additional involvement of further basal ganglia structures which have been suggested to be essential for planning and releasing the speech motor program [e.g. 25]. Considering the obvious essential role of the basal ganglia for basic speech motor processing, one might expect abnormal patterns of activation in PD, however, functional imaging data on speakers with PD are sparse. Recent fMRI analyses of the speech motor network in Parkinsonian patients led to the hypothesis of fading speech motor representations which seemed to be insufficiently updated by external auditory feedback [26]. Moreover, according to those neuroimaging studies, Parkinsonian dysthria was found to be related to an altered recruitment of orofacial motor cortex and cerebellar circuits and an increased involvement of the premotor prefrontal cortices, especially in the non-medicated condition [27,28]. Some of these abnormal activation patterns have been interpreted as compensatory phenomena to preserve speech or – alternatively – as a specific modification of the physiological activation pattern as a consequence of the neurodegenerative process of PD [e.g. 29,30]. However, the interpretation of these findings still bears some difficulties, and another recent fMRI study questioned the modulation of task-dependent cerebral networks by dopaminergic treatment [31].

Summarized, the pathophysiological scaffolding for the abnormal patterns of basic motor speech performance observed in our study is still a matter of debate. In our study, the majority of patients were in H&Y stage 1.5 or 2 which means mild to moderate motor impairment, however, with already present axial symptoms (e.g. akinesia and/or rigidity of neck and facial muscles, disturbed posture and/or gait) which clinically indicates bilateral neurodegeneration of the substantia nigra as some supposed predisposition for motor speech impairment. In a previous study on PD patients

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Table 3
Comparison between control and PD.

<table>
<thead>
<tr>
<th></th>
<th>Control group n = 32</th>
<th>Entire PD group n = 50</th>
<th>PD subgroup n = 32</th>
<th>t-Test vs. entire PD group/vs. PD subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKT</td>
<td>16,726 ± 8278</td>
<td>15,629 ± 7298</td>
<td>13,510 ± 6248</td>
<td>n.s./n.s.</td>
</tr>
<tr>
<td>maxSylRep</td>
<td>3.72 ± 1.33</td>
<td>4.27 ± 1.06</td>
<td>3.79 ± 0.98</td>
<td>p = 0.044/n.s.</td>
</tr>
<tr>
<td>COVmax1</td>
<td>1.00 ± 0.28</td>
<td>1.60 ± 0.89</td>
<td>1.92 ± 0.96</td>
<td>p &lt; 0.001/p = 0.001</td>
</tr>
<tr>
<td>%PA</td>
<td>1.62 ± 3.07</td>
<td>2.64 ± 3.59</td>
<td>2.79 ± 3.98</td>
<td>n.s./n.s.</td>
</tr>
<tr>
<td>avIntDur</td>
<td>467 ± 176</td>
<td>498 ± 207</td>
<td>466 ± 176</td>
<td>n.s./n.s.</td>
</tr>
<tr>
<td>COVmax2</td>
<td>0.96 ± 0.35</td>
<td>–</td>
<td>1.64 ± 1.03</td>
<td>–/p = 0.001</td>
</tr>
<tr>
<td>COVmax3</td>
<td>1.05 ± 0.44</td>
<td>–</td>
<td>1.76 ± 0.81</td>
<td>–/p = 0.001</td>
</tr>
<tr>
<td>pa–ti ratio</td>
<td>0.987 ± 0.06</td>
<td>–</td>
<td>0.936 ± 0.01</td>
<td>–/p = 0.015</td>
</tr>
</tbody>
</table>
with more advanced motor impairment [12], correlations were found between impairment of syllable repetition and the axial sub-score of the UPDRS motor score. This finding was interpreted as some hint for the involvement of non-dopaminergic neurotransmitter dysfunctions. Interestingly, our investigation revealed the same pattern of dysfunctional syllable repetition already in patients with Ho/Y stage 1, however, in a rather small subgroup of n = 9 patients. Given that these findings are reproducible in a larger group of patients this could be a hint for non-dopaminergic (speech motor) dysfunction already present in the very early motor stages of PD. The detection of such abnormalities could be a very helpful “piece in the diagnostic puzzle” where every single clinical sign and symptom can be essential for the establishment of the diagnosis.

5. Conclusion

Investigation of pace and steadiness of syllable repetition is an easily applicable, non-intrusive and cost effective method which reveals significant abnormalities of basic motor speech performance in patients with very mild to moderate motor stages of PD. Further longitudinal studies are warranted, ideally performed in drug-naïve patients with very discrete motor symptoms to survey, if the proposed method can become a helpful diagnostic tool for the early diagnosis of PD and can give some interesting insights into the underlying pathophysiology.

Authors contribution

Dr. Skodda involved in the study concept and design, acquisition and analysis of data, statistical analysis, conception and writing of the manuscript. All authors have read the manuscript, and the paper has not previously been published and is not under simultaneous consideration by another journal. There has been no ghost writing by anyone not named on the authors list.

Disclosures and conflicts of interest

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References