Intonation and Speech Rate in Parkinson's Disease: General and Dynamic Aspects and Responsiveness to Levodopa Admission

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Summary: Objective. The aim of our study was the analysis of fundamental frequency (F_0) variability (fundamental frequency standard deviation [F_0SD]) and net speech rate (NSR) in the course of reading in Parkinsonian patients' speech, with special emphasis on the changes of F_0SD and NSR from the first to the last sentence of the task.

Patients and Methods. We examined 138 patients with Parkinson's disease (PD) and 50 age-matched control persons using a standardized reading task with subsequent acoustical analysis of F_0SD and NSR. A subgroup of 20 PD patients underwent a standardized levodopa challenge.

Results. F_0SD in PD patients was significantly reduced compared with the control group when based on the measurement of the entire reading task. Furthermore, in the PD group, NSR and F_0SD showed significant changes from the first to the last sentence of the reading task, but no correlation was seen between NSR and F_0SD. Standardized levodopa administration had no effect on NSR and F_0SD when related to the entire reading passage, but the aforementioned decline of F_0 variability in the course of reading seemed to be counterbalanced by levodopa administration.

Conclusions. In this large series of PD patients, previous findings of reduced F_0SD in PD were confirmed. Additionally, this is the first analysis to show an increasing reduction of F_0 variability in the course of reading mirroring abnormalities in the dynamical aspects of speech in PD. According to the results of the levodopa challenge, dopaminergic stimulation seems to ameliorate dynamic intonation changes over time, whereas overall intonation variability might be a PD symptom independent of dopaminergic control.

Key Words: Parkinson's disease–Hypokinetic dysarthria–Dysprosody–Speech impairment–Levodopa challenge–Motor speech performance–Motor instability.

INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons, primarily in the substantia nigra pars compacta.[1] Additionally, there is a growing body of evidence that the caudal brain stem nuclei and other nondopaminergic neurons may be affected long before the classic loss of dopaminergic neurons.[2] From the clinical field of vision, motor impairment as muscular rigidity, tremor, and bradykinesia are the most ostensible dopaminergic symptoms, but the great majority of individuals with PD develop further voice and speech problems over the course of their illness, which commonly are interpreted as the manifestation of bradykinesia on the laryngopharyngeal tractus.[3] Based on the perceptual analysis of large samples of Parkinsonian speakers, first systematic research on Parkinsonian speech defined salient clusters of deviant speech dimensions in hypokinetic dysarthria, including a harsh breathy voice quality, reduced variability of pitch and loudness, reduced stress, imprecise consonant articulation, and short rushes of speech interrupted by inappropriate periods of silence.[4,5]

Hypokinesia of the voice apparatus has been presumed to be the major pathomechanism of monopitch speech and altered speech rate in PD, leading to an "undershooting" of articulatory gestures.[6–8] Previous research on prosody indicates a significantly reduced fundamental frequency (F_0) variability in PD patients compared with healthy controls,[4,9–12] whereas studies on overall speech rate remained inconclusive.[7–10,13] If hypokinesia of the voice apparatus is the major pathomechanism of monopitch speech in PD, as it is supported by some previous studies,[3,14] F_0 variability should ameliorate after levodopa admission and should show some further decline in the course of the disease progression. However, data on F_0 variability does not unequivocally confirm an association of monopitch speech and dopaminergic transmission in PD. Although some authors reported on an amelioration of reduced F_0 variability in PD patients after levodopa administration[15] or on a further decline in the course of the disease,[16] other studies failed to demonstrate a correlation between F_0 variability and disease severity,[13] a constant response to dopaminergic therapy,[17–20] or a correlation between F_0 variability and general motor symptoms in PD.[19]

On the other hand, independent from the hypothesis of hypokinesia as the main causation of "undershooting" of articulatory gestures, speech performance can be interpreted as a series of skilled motor gestures requiring upstream central coordination as motor planning and programming, which are critically mediated by cerebral networks. Movement preparation is characterized by a sustained premovement supplementary motor area (SMA) neural discharge and is thought to contribute to cortical motor set, which allows the forthcoming movement to be normally executed.[21] During the execution phase of movement, tonic SMA and phasic discharges from

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the globus pallidus (GP) interact to effect the smooth execution of automatic skilled movement by means of the basal ganglia–thalamocortical motor circuit. Furthermore, the GP is critically involved in the internal release of each submovement within a motor sequence.[22] Once the first submovement is executed, the GP would produce a phasic burst of activity to trigger the crisp termination of SMA set-related preparatory activity and the release of the next submovement, while permitting set-related activity for the following submovement to commence. Hence, the entire skilled movement sequence can be automatically run to completion.[23] In PD, faulty GP phasic output to the SMA may lead to abnormal preparatory activity, resulting in submovements that are slow and reduced in amplitude. These impairments may compound as the sequence progresses, resulting in "motor instability." Therefore, the amplitude of submovements can show a further decrease as the execution of the sequence progresses. This sequencing effect (also known as "motor instability") refers to the inability to maintain the preset amplitude for each submovement[24,25] and is thought to be relevant not only for the control of the upper and lower limbs, but also for the control of speech intensity.[26]

The aim of this study was to analyze F_0 variability in a standardized reading task in a representative number of PD patients independent from clinical manifestation of dysarthria. In addition, F_0 variability and speech rate were analyzed in the course of reading to find possible abnormalities in the dynamic aspects of prosody over time as a manifestation of "motor instability" related to the modalities of pitch and speech rate. A small subgroup of patients underwent a standardized levodopa challenge to evaluate the effect of short-term dopaminergic medication on F_0 variability and speech rate.

PATIENTS AND METHODS

Each participant had to perform a standardized reading task composed of four complex sentences (see Appendix). In addition to the analysis of intonation variability of the entire text, the four sentences were analyzed separately and compared with each other for further description of F_0 variability and speech rate behavior in the course of reading. Furthermore, as each of the four sentences was composed of a main clause and a subordinate clause, F_0 variabilities of main and subordinate clauses were separately measured to detect further changes of F_0 variability on the segmental level. To exclude difficulties in reading, the participants had to read the text twice; the second sequence was taken for the definite analysis.

Speech samples were digitally recorded in a quiet room with a sample rate of 44 100 Hertz (Hz) using a commercial audio software (Steinberg WaveLab; Steinberg, Hamburg, Germany) and a head-set microphone (Plantronics Audio 550 DSP; Plantronics Inc., Santa Cruz, CA). Description of intonation was based on the F_0 measurement using a special speech software (*PRAAT* [www.praat.org / Phonetic Sciences, University of Amsterdam, The Netherlands])[27] extracting F_0 from the speech sample as the lowest audio frequency with the highest intensity and less harmonic contents.[28] F_0 variation was declared as F_0 standard deviation (F_0SD), in Hz. The difference between F_0SD of the first and fourth sentences was defined as ΔF_0SD (Figure 1). Analysis of speech rate was performed by measuring the length (in milliseconds) of each syllable and each pause (defined as silent period lasting at least 10 milliseconds), based on the oscillographic sound pressure signal. Speech rate was defined as net speech rate (NSR; syllables per second related to net speech time). The difference between NSR of the first and fourth sentences was defined as "articulatory acceleration" (AA).

As a simple parameter for speech breathing, each participant was asked to keep the German vowel /a/ as long as possible on one breath, defined as maximum phonation time (MPT). MPT was performed twice, and the longest MPT of the two attempts was taken for the further analysis.

The examiner who conducted the definite acoustical analysis (W.G.) was blinded to participants' condition. The results of the computerized pitch analyses were checked by an auditory control to eliminate artifacts or background noises. To evaluate the test-retest reliability, 40 participants (15 controls and 25 PD

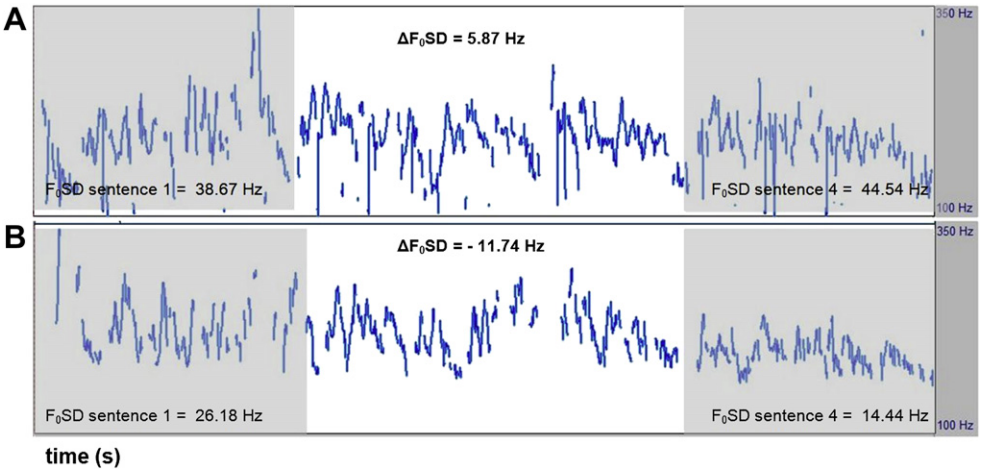

FIGURE 1. Fundamental frequency (F_0) contour in the course of reading and comparison of F_0SD of the first and the last sentences in a healthy speaker (**A**) and a Parkinsonian patient (**B**).

patients in their best "on" state) had to run consecutively through the speech task for two times. As satisfying test-retest reliability was found ($r = 0.854$–0.898, $P < 0.001$), only one single-speech-task cycle was performed for the definite study.

The study included 138 PD patients (78 males and 60 females) after written informed consent according to a positive vote of the ethic committee of the Ruhr-University Bochum. Patients' ages ranged from 42 to 84 years (mean = 66.74; median = 68; SD = 8.48). Idiopathic PD had been diagnosed from 1 to 30 years before recording (mean = 6.54; median = 5; SD = 5.32) based on UK Parkinson's Disease Society Brain Bank Criteria.[29] Each patient underwent a neurological examination according to Unified Parkinson's Disease Rating Scale - Motor Score (UPDRS III)[30] (ranging from 5 to 61 points; mean = 22.96; median = 22.5; SD = 11.84) and was staged according to Hoehn and Yahr scale (H&Y)[31] (ranging from 1 to 4; mean = 2.60; median = 2.5; SD = 0.71) before performing the speech task. At the time of the examination, patients were in a stable "on" state with dopaminergic medication unchanged since at least 4 weeks before the examination. Speech and motor examinations were performed 60–90 minutes after the morning dose of medication to ensure the "on" state. None of the patients experienced orofacial or abdominothoracal dyskinesias while being tested, based on clinical observation during the examination to exclude dyskinesia-related speech impairment.[32] Because the aim of the study was the acquisition of objective intonation parameters, perceptual analysis of clinical manifestation of dysarthria in PD patient was not carried out.

As control group, 50 healthy persons (24 males and 26 females), ranging from 43 to 80 years of age (mean = 65.64; median = 66.5; SD = 8.98), were tested. As gender was found to influence the results (see later), a gender-based comparison between the PD group and the control group was performed. Age distribution showed no significant differences between the groups.

In 20 PD patients of this series (median age = 64.65 years, range = 49–77; seven males and 13 females), a standardized levodopa challenge was carried out with the administration of 200 mg of soluble levodopa after withdrawal of medication for at least 12 hours. UPDRS motor scale and speech tasks were performed in a defined "off" state and again in the best "on" state 30–45 minutes after levodopa admission. None of these patients experienced orofacial or abdominothoracic peak-dose dyskinesia.

Statistics

Winstat (R.Fitch Software, Bad Krozingen, Germany) was used for statistical analyses. The level of significance was set at $P = 0.05$. Analyses of variance (ANOVA) with gender and condition (PD vs control) as between-subject factors and of age as intrasubject factors were performed first.

For comparison of means of speech parameters between PD patients and controls, *t* test for independent samples was used, as the variables were widely normally distributed (Kolmogorov-Smirnov test). Analysis of variance and *t* test for dependent samples were used for intragroup comparison of the single sentences and the different parts of sentences. Bonferroni adjustment was performed to compensate for multiple testing. Pearson correlation was used to test for significant correlations.

RESULTS

Participants' characteristics and detailed numerical data are listed in Tables 1–3.

According to ANOVA, gender and condition were significant factors ($P < 0.01$) for mean F_0, F_0SD, and NSR, whereas age was not. Therefore, the subsequent analyses were performed separately for male and female subgroups.

In both male and female Parkinsonian patients, F_0SD continuously declined from sentence 1 to 4, with the most explicit differences seen in the direct comparison between sentence 1 and sentence 4. Therefore, the definite statistical analysis was only performed on sentence 1 compared with sentence 4 to avoid the problem of multiple testing.

When related to the subsentence level of F_0 variability, there were no significant differences comparing F_0SD of the main clause with the following subordinate clause, neither in the PD nor in the control group. Therefore, these data were not displayed in the results tables.

Both in male and female Parkinsonian patients, F_0SD was found to be reduced compared with the accordant control group when related to the entire reading task (male: $P < 0.05$; female: $P < 0.0001$) and when separately related to sentence 1 and sentence 4 as well, at least in the female subgroup (sentence 1: $P < 0.001$, sentence 4: $P < 0.001$). In the male subgroup, only F_0SD of sentence 4 showed a significant reduction in the PD group ($P < 0.01$). In both PD groups, there was a significant decrease of F_0SD in sentence 4 compared with sentence 1 ($P < 0.01$), which was not seen in the control groups. ΔF_0SD was significantly higher in PD patients compared with the controls ($P < 0.001$). Compared with the accordant control group, mean F_0 was elevated in the male PD group but not in the female group. There were no significant differences of NSR in the PD patients and the controls, but AA showed a tendency toward elevation in female PD group, although without statistical significance ($P = 0.056$).

In the Parkinsonian patients, NSR showed no correlation with F_0SD neither when related to the entire speech task nor when related to the single sentences. Likewise, no correlation was seen between ΔF_0SD and AA. There was no correlation between MPT and the other speech parameters. In the male PD patients, disease duration and H&Y stage showed no correlation with the speech variables, whereas UPDRS III showed a weak negative correlation with NSR ($r = -0.213$, $P = 0.037$). In the female PD group, disease duration showed a weak negative correlation with NSR ($r = -0.274$, $P = 0.021$). Both H&Y stage and UPDRS III were negatively correlated with F_0SD ($r = -0.320$, $P = 0.010$ and $r = -0.477$, $P < 0.001$, respectively). No correlation was seen among F_0SD, ΔF_0SD, NSR, and AA, and MPT in the male and female control group.

TABLE 1.
Participants' Characteristics

Characteristics	PD Group (78 Males and 60 Females)	Control Group (24 Males and 26 Females)	Comparison of Control vs PD Group
Age (years)	Male: mean = 66.37; SD = 7.23; range = 44–81	Male: mean = 65.83; SD = 8.66; range = 43–78	NS
	Female: mean = 67.23; SD = 9.41; range = 42–84	Female: mean = 65.46; SD = 9.44; range = 47–80	NS
Duration	Male: mean = 6.59; SD = 4.93; range = 1–19		
	Female: mean = 6.47; SD = 5.83; range = 1–30		
UPDRS III	Male: mean = 22.92; SD = 11.67; range = 5–60		
	Female: mean = 23.02; SD = 12.16; range = 6–61		
Hoehn and Yahr	Male: mean = 2.59; SD = 0.60; range = 1.5–4		
	Female: mean = 2.61; SD = 0.83; range = 1–4		
MPT (ms)	Male: mean = 13 028; SD = 3960; range = 3160–24 700	Male: mean = 14 293; SD = 7893; range = 5030–40 100	NS
	Female: mean = 10 320; SD = 4365; range = 2100–24 100	Female: mean = 11 003; SD = 5187; range = 3050–27 150	NS

Abbreviation: NS, not significant.

In 20 PD patients (seven males and 13 females) of this series, a standardized levodopa challenge was carried out with significant improvement of motor performance (UPDRS III off medication: mean = 33.00, SD = 13.37; UPDRS III on medication: mean = 18.70, SD = 8.50; $P < 0.001$). However, there were no differences of F_0SD (in male and female patients) after levodopa administration when related to the entire reading task and when related to sentence 1 and sentence 4 as well. However, in the male and female PD patients, the decrease of intonation variability in the course of reading, as measured by comparison of sentence 4 and sentence 1 ($P < 0.05$), was no longer seen after dopaminergic stimulation, although ΔF_0SD in the "on" and "off" state showed no significant differences in both gender groups probably because of the small sample sizes. No significant influence of levodopa admission on NSR and AA was seen, but at least in the female patients, AA showed a trend toward reduction in the "on" state ($P = 0.079$). Detailed numerical data are listed in Table 4.

DISCUSSION

In Parkinsonian dysarthria, significant differences concerning degree and kind of prosodic disturbance exist. Therefore, the aim of the present study was the measurement of F_0 variability and speech rate in the course of the speech performance to test the hypothesis, if the phenomenon of "motor instability"

TABLE 2.
Comparison Between Male Parkinsonian Patients and Controls

	PD Group (n = 78)	Control Group (n = 24)	Comparison of Control vs PD Group
Male	Mean/SD	Mean/SD	*P* Value
Mean F_0 (Hz)	130.18/21.83	117.16/15.59	0.010
F_0SD (Hz)	14.96/4.61	18.01/6.23	0.022
F_0SD_sen1	14.82/4.75**	16.10/5.64 (NS)	NS
F_0SD_sen4	12.62/3.91**	16.77/6.48 (NS)	0.006
ΔF_0SD (Hz)	−1.20/2.13	0.67/3.62	0.0001
NSR (syllable/s)	5.24/0.80	5.16/0.50	NS
AA	0.29/0.35	0.26/0.42	NS

Abbreviation: NS, not significant.
**$P < 0.01$ refers to the intragroup comparisons.

TABLE 3.
Comparison Between Female Parkinsonian Patients and Controls

	PD Group (n = 60)	Control Group (n = 26)	Comparison of Control vs PD Group
Female	Mean/SD	Mean/SD	*P* Value
Mean F_0 (Hz)	191.03/22.88	192.58/20.62	NS
F_0SD (Hz)	21.32/5.89	34.48/11.52	<0.0001
F_0SD_sen1	21.18/5.79**	30.00/11.73 (NS)	0.001
F_0SD_sen4	18.02/4.89**	31.26/11.77 (NS)	<0.0001
ΔF_0SD (Hz)	−3.15/2.85	1.26/3.39	<0.0001
NSR (syllables/s)	5.10/0.57	5.26/0.47	NS
AA	0.32/0.49	0.15/0.32	NS ($P = 0.056$)

Abbreviation: NS, not significant.
** $P < 0.01$ refers to the intragroup comparisons.

originally described for limb movement abnormalities[33] is also present in Parkinsonian dysarthria.

First, the data confirmed previous studies with a demonstration of a significant reduction of F_0SD in male and female PD patients compared with the accordant age- and gender-matched control group. Patients performed a standardized reading task to achieve comparable data for the acoustical analysis, although it is known that prosody might be influenced by the kind of speech task. Results of previous studies had revealed a higher F_0 variability in reading or deliberately "clear" or "emotional" speech compared with conversational speech in PD patients and in healthy speakers as well, as external cues are known to influence prosodic parameters.[4,34–36] Therefore, the present data on F_0 variability while reading should presumably mirror the maximum remaining intonational repertoire in the bounds of PD, whereas conversional speech—although not tested in this study—is likely to engender an even lower F_0 variability.

Correlations between disease duration and UPDRS Motor Score on the one hand and F_0 variability and speech rate on the other hand were different between male and female PD patients. These findings may contribute to some differential impact of the disease on speech in men and women, which is affirmed by previous studies and underlines the necessity of gender-based comparison in the analysis of speech.[37]

UPDRS Motor Score showed a negative correlation with F_0SD at least in female PD patients. This finding seems to affirm the hypothesis of abnormally restricted F_0 being just one

TABLE 4.
Comparison of Speech Parameters Before and After Levodopa Administration

	Off	On	Comparison of Off vs. On Medication
Levodopa Challenge	Mean/SD	Mean/SD	*P* Value
Male (n = 7)			
UPDRS III	34.14/13.04	18.71/7.91	0.002
F_0SD (Hz)	14.76/3.23	13.88/4.00	NS
F_0SD_sen1	13.88/2.22*	12.87/2.86 (NS)	NS
F_0SD_sen4	11.71/2.61*	12.48/5.21 (NS)	NS
ΔF_0SD (Hz)	−2.17/2.02	−0.39/3.73	NS ($P = 0.081$)
NSR (syllables/s)	5.62/0.71	5.90/0.80	NS
AA	0.58/0.82	0.68/0.35	NS
Female (n = 13)			
UPDRS III	32.38/14.03	18.69/9.12	0.001
F_0SD (Hz)	19.02/4.73	18.65/4.61	NS
F_0SD_sen1	18.57/3.49*	19.02/4.73 (NS)	NS
F_0SD_sen4	16.72/4.14*	18.56/5.00 (NS)	NS
ΔF_0SD (Hz)	−1.85/3.38	−1.70/4.51	NS
NSR (syllables/s)	5.31/0.49	5.26/0.45	NS
AA	0.33/0.48	0.08/0.20	NS ($P = 0.079$)

Abbreviation: NS, not significant.
* $P > 0.05$ refers to the intragroup comparisons.

further manifestation of hypokinesia as other Parkinsonian motor symptoms. However, although global motor function responded to levodopa challenge performed on a subgroup of our series, F_0 variability related to the entire reading passage did not ameliorate after short-time levodopa admission. In fact, the effect of dopaminergic stimulation on overall speech parameters and dysprosody, in particular, remains inconclusive. Although some authors found no effect of dopaminergic therapy on speech rate, prosodic and phonation parameters[15,18–20,38], and overall intelligibility,[17,39] others describe a positive levodopa effect on tongue strength and an improvement of speech intelligibility assessed by perceptual analysis in PD patients.[40,41] To explain the findings of the levodopa challenge in the actual study, different interpretations are possible. First, impaired F_0 variability might be one of the nondopaminergic symptoms of PD only, paralleling general motor impairment (measured by UPDRS III) without sharing the same underlying pathophysiology. Second, pitch variability might be a Parkinsonian feature responding only to long-term dopaminergic stimulation.

In addition to the confirmation of a general reduction of F_0 variability in Parkinsonian speech, the present study brought out some further insight into the dynamic aspects and microstructure of F_0 variability in the course of reading. According to the actual data, there is a significant decline of F_0SD in the course of reading, especially when comparing the last sentence of a given reading passage with the initial sentence, which, to the best we know, has never been examined in previous studies. Although it was likely to find again the same phenomenon of decreasing F_0SD on the subsentence level when comparing different segments of a composed sentence, these expectancies were not confirmed. Although the segmental organization of speaking and reading has to follow some linguistic demands, participants were free to unitize the complex sentences according their own natural speech rhythm. Therefore, the comparison of F_0 variability of the main and the subordinate clauses—as it was performed in the present study—could be too simplistic and does not respect the individual patterns of subdividing composed sentences. Because changes of speech rhythm have been shown to occur in PD patients,[13] this might be the reason for the absence of a reproducible behavior of F_0SD in the course of the single sentence.

The phenomenon of declining F_0SD in the course of reading when related to the sentence level cannot be caused by impaired speech breathing alone (as there was no correlation with MPT). It rather might be interpreted as an insufficiency to maintain a motor speech impulse in the course of a given speech task, possibly as an indication of impaired temporal motor planning in the anticipation of the imminent end. Because the present study additionally confirmed the tendency of AA in the course of reading—although without statistically significant differences to the control speakers—which has previously been described in a large series of PD patients,[13] one might suppose a shared underlying pathophysiology resulting from dysfunctional execution of motor programs caused by basal ganglia impairment[42] and leading to a general "undershooting" of articulatory gestures and motor instability.[7,8] However, as there was no correlation between the decrement of F_0SD and the extent of AA, both phenomena seem to be under a different pathophysiological control.

Interestingly, there was a tendency toward the improvement of the F_0 variability decline in the course of reading after levodopa administration, but admittedly, the number of participants was too small to carry out a powerful statistical analysis. Presupposed that this tendency was reproducible in a larger levodopa challenge sample size, the effect of dopaminergic stimulation on Parkinsonian intonation might be rather a stabilization of F_0 variability in the course of performing than an amelioration of monopitch speech on average, which has already been hypothesized for the aspect of speech intensity before.[19]

Exhaustion of intonation variability in the course of reading bears a resemblance to further characteristic motor features in PD as typical changes in handwriting[43] (so-called "micrographia") or rising fatigue in the performance of rapid alternating movements.[44] The phenomenon of declining amplitude in the course of a repetitive motor performance observed in PD patients might refer to an impairment of internal cueing and of maintaining generally highly automated motor sequences as a course of basal ganglia dysfunction.[24,25,33,45] Further studies are warranted to search for correlations between the phenomena of motor instability in different modalities as speech and limb movements in PD to gain further insight into the underlying and shared pathophysiological mechanisms.

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